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ERRATA

The following are the legends which should have appeared under the illustrations of the article entitled The Effect of Parathyroid Extract and Liver Extract on the Hypertension Produced by Guanidine Compounds, by Ralph H. Major and C. R. Buikstra, on pages 392 to 399, in the December issue of the Johns Hopkins Hospital Bulletin:

FIG. 1 (*p. 393*). Curve showing lack of effect of Hanson's parathyroid extract upon normal blood pressure. Weight of dog 12 kilos. Injected intravenously.

FIG. 2 (*p. 394*). Curve showing lack of effect of Collip's parathyroid extract upon normal blood pressure. Weight of dog 10 kilos. Injected intravenously.

FIG. 3 (*p. 395*). Curve showing effect of Hanson's parathyroid extract upon the hypertension produced by methyl guanidine sulphate.

FIG. 4 (*p. 396*). Curve showing effect of Collip's parathyroid extract upon the hypertension produced by methyl guanidine sulphate.

FIG. 5 (*p. 397*). Curve showing effect of liver extract upon normal blood pressure. Note transient effect. Two injections of 5 cc. each.

FIG. 6 (*p. 397*). Curve showing effect of liver extract upon the hypertension produced by methyl guanidine sulphate. Blood pressure lowered and continued so for 1 hour.

FIG. 7 (*p. 398*). Curve showing effect of liver extract upon the hypertension produced by methyl guanidine sulphate. Blood pressure lowered and continued so for 2 hours.

PULMONARY TUBERCULOSIS AND PREGNANCY[1]

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Medical literature is filled with articles on the significance of pulmonary tuberculosis during pregnancy and the subject has been treated extensively from various points of view. But when one considers the results, there is a singular discrepancy in the conclusions, and the practising physician is still left in doubt. Nearly every paper attempting a definite conclusion is followed within a few months by a specific denial with case results from a contemporaneous writer. The argument often becomes hot and the reader is forced to discount the results when an author lauds his own medical qualifications and criticizes the lack of ability of his antagonist.

Perhaps an important reason for disagreement lies in the remarkable lack of association between obstetrics and medicine. Through their patients internist and surgeon are brought together. The diagnosis of a gastric ulcer and the therapeutic procedure represent, in general, the balanced conclusion of the surgeon and the practitioner, a significant indication of association of two branches of the art of medicine. The surgeon is becoming accustomed to having a careful medical examination made of all but his emergency cases before operation, not only from the point of view of diagnosis, but also with the idea of surgical risk and future prognosis in his mind. The simple operation for appendicitis is much less frequently done today than a decade ago, because of knowledge afforded by the practitioner —the subsequent aftermath of symptoms that may develop through abdominal adhesions, and the fact that in many cases the condition will take care of itself. Conservatism is the order of the day and it is quite probable that it represents the average conclusion and not

[1] Read before the Johns Hopkins Medical Society, April 27, 1925.

a swinging of the pendulum. At all events, it is an undoubted fact that not since the onset of the age of specialization has there existed so close coöperation between medical man and surgeon as is found today.

It is unfortunate for patients that medicine and obstetrics have not been drawn into this "pooling" of knowledge. In the large hospitals there is to be seen an improving medical examination of obstetrical patients, but the routine physical examination is made by the interne who has just graduated and whose main interest is in his life's work—the practice of obstetrics. Time is short, and success in his major subject necessitates long and irregular hours, so that the physical examination of his patients is relegated to the routine of the day, after his obstetrical work is completed. To be sure, the interest of the head of the department and the presence of assistants with unusual medical training modify the procedure in various hospitals. But even in the best clinics, only the gross thoracic lesions are picked out for medical consultation, and the follow-up system even for these cases is very faulty. Too often, then, in hospitals as well as in outside practice, the general physical examination of obstetrical patients will include only a general look at the patient, a rapid auscultation of the heart and apices of the lungs and practically no history beyond a report of previous deliveries. It would be impossible for some cases of early tuberculosis and heart disease not to escape detection, and it would be remarkable if the obstetrician did not fail to warn some of his patients about the danger of subsequent pregnancies or of too rapid fecundation. This is not said critically, for the practical difficulties of obtaining the ideal are all too well recognized. But it is certainly true that the striving towards the ideal would bring the obstetrician and those primarily interested in internal medicine into much closer association. That the patient would be benefited is clearly indicated by reading obstetrical histories containing medical consultations in cases of heart disease or tuberculosis. The death rate among the mothers and children is altogether too high, according to the obstetricians, and is the subject of various crusades. We believe that an important method of attack is with the aid of those whose especial interest lies in internal medicine.

It is possible, therefore, that the medical practitioner's ignorance in things obstetrical, and the obstetrician's lack of training in thoracic problems, is one reason for the contradictory conclusions concerning the tuberculous pregnant woman. But there is a second factor which we think is of equal significance—the social status, or better, the financial resources of the patient. *The great essential in the treatment of tuberculosis is rest*, and provision for it must be made the basis of all therapeutic procedures. Food, sunlight, altitude, humidity, are of relatively little importance as compared with the fundamental need of rest in bed. After the acute stage, the average tuberculous patient is able to perform various activities, provided that she reserves hours for rest in bed during the day, and provided there is protection against fatigue. And this is doubly true for the pregnant woman with tuberculosis. Again, in general, the normal woman, after becoming pregnant, continues the routine of her daily life. The physical work of the ordinary housewife is extensive enough—drudging, uninteresting routine that is never done—and her few moments of so-called rest are filled with sewing and knitting that afford her mind a chance to worry over the problems concerning her family and herself. Pregnancy, therefore, becomes an additional drain on a physical bank account that is always in danger of being overdrawn. On the other hand, there are women, mentally so constituted and financially so situated, who, at the onset of pregnancy, can give up the entire day to the business of taking the best possible care of themselves, and can forego entirely the work that previously has been demanded of them. If, now, these generalizations are applied to the tuberculous pregnant woman, is there not an obvious explanation for some of the contradictory reports on the influence of pregnancy on tuberculosis? The woman whose pulmonary lesion is just kept in check, while she is doing her daily work, will not be able to prevent its advance if pregnancy is superadded. This is not medical knowledge but common sense, and represents a situation which must be met, and which at present is, in general, only a theoretical ideal. On the other hand, as some writers claim, the pregnant woman with tuberculosis is sometimes greatly improved in her lung condition if she can get six months' rest, and that in spite of the pregnancy. Moreover, in getting this rest or anti-tuberculosis therapy,

it is better if the nervous, worrying housewife can be taken from her surroundings, since the mental worry from servants, children and telephone, with their problems, is nearly as harmful as actual physical work. Thus, it would seem that the financial status of the patient, the accessibility of sanitaria and the patient's nervous temperament, are factors that enter into the conclusions offered by different authors and constitute factors in the "individualizing" of patients.

Our study is based on the review of the first 14,000 histories of the in-door obstetrical service of the Johns Hopkins Hospital. The study has been handicapped greatly by insufficient notes, both in regard to history and physical examination, particularly in the earlier cases. (In late years these notes have been greatly improved.) And further, the lack of reports subsequent to delivery in many cases is unfortunate. In numerous instances, however, search through the records of the medical dispensary, or of the Phipps Clinic for tuberculosis, has produced the after history of those patients whose attendance for personal examination was impossible. But these difficulties in getting a sufficiently large number of cases have led us to continue visits to the obstetrical wards and dispensary, so that at some later time a further detailed report will be available, which will greatly supplement our investigations of the past two and a half years.

In this series of cases the obstetrical cards give 134 patients who were grouped as having pulmonary tuberculosis in one or more of its various forms. It would be interesting to speculate from this number as to the prevalence of tuberculosis among women of the child-bearing period. But such an effort would necessitate classifying the patients according to age, color and decade of disease incidence, and would reduce the individual group to such small numbers that any conclusion would be useless. Suffice it to say that this number roughly corresponds to the morbidity percentage of Baltimore city as obtained from the Health Department. In other words, the physical examinations by the obstetrical staff at this hospital, according to these figures, suggest an incidence rate of tuberculosis closely approximating that reported by the physicians of the city, which is, in all probability, definitely below the actual figures. One

may draw only suggestive conclusions as to the effect of pregnancy on the morbidity percentage, from such small numbers, but it is worth pointing out that this population of 14,000, equally divided among whites and blacks and including a large number of multiparae, shows no increase over the expected incidence of pulmonary tuberculosis, and that the routine physical examination discloses no alarming percentage of tuberculosis during the period of gestation. This is a fair statement, since, as a rule, the patients were seen periodically in the dispensary during the later six months of pregnancy and on the wards during labor and at least for the first two weeks of the puerperium. So then, although we believe that gestation and the puerperium may serve as the final factor to "break down" patients who have tuberculosis, we can find no evidence that pregnancy in any way promotes the incidence rate. And when one remembers that the child-bearing age of women corresponds to that age period in which pulmonary tuberculosis ordinarily appears, even without pregnancy, and that the incidence rate at this age is definitely below the male incidence rate, except between the ages of twenty and thirty, one wonders whether the association of tuberculosis and pregnancy has not been exaggerated, and whether it is not in great part coincidental. If it be conceded that tuberculosis in adults is the development of a disease contracted in childhood, then it would appear that, though gestation may precipitate activity of tuberculous lesions, the actual incidence rate of tuberculosis is not higher for women who have borne children than for those who have not. Reliable statistics on the relation in incidence rate of tuberculosis between pregnant and non-pregnant women would be of great interest, but are still lacking.

Our 134 patients may be grouped as follows:

1. Those with questionable tuberculosis.
2. Those with definite but inactive pulmonary tuberculosis.
3. Those with definite active tuberculosis of the lungs upon whom therapeutic abortion was not performed.
4. Those with definite tuberculosis of the lungs upon whom therapeutic abortion was induced.
5. Those with pulmonary tuberculosis associated with other diseases.

Each of these groups will be taken up separately.

1. PREGNANCY WITH QUESTIONABLE TUBERCULOSIS

In the first there are 50 cases. Since the diagnosis of tuberculosis in these patients was questionable, definite conclusions cannot be drawn from their study. All of them were noted on the obstetrical histories as having abnormal physical signs—slight percussion change, indefinite râles, or modified breath sounds. Several of them were subsequently reëxamined by physicians particularly interested in tuberculosis and the signs were reported as equivocal or negative. Some of these patients had tuberculous family histories and three gave a history of haemoptysis. In 10, subsequent careful examination disclosed no suspicious signs, and, since all of them went through labor and the early puerperium with no unusual elevation of temperature, it is probably safe to say that none of this group had active tuberculosis and that only a very small proportion had any actual pulmonary involvement. It would seem that every such patient should have been given a careful examination from the point of view of tuberculosis and that her history should have contained a follow-up note as to the lung findings 6 or 12 months later.

These 50 patients had 45 healthy normal babies, whose birth-weight average was 3432 grams, which compares more than favorably with a birth-weight average of 3297 grams in 100 consecutive normal deliveries on the same service. There were 4 spontaneous abortions or premature births and one baby died at birth, which again compares favorably with the record of the 100 normal cases, in which there were 4 abortions or premature births and 7 babies still-born or who died during the first two weeks of the puerperium. The subsequent histories and examinations of these babies, so far as obtained, did not indicate that they had contracted tuberculosis.

We feel, therefore, that as regards these 50 patients, there is not sufficient evidence to say that they had tuberculosis. There is one feature to which we would call attention. The total number of cases diagnosed as tuberculous on the obstetrical ward is 134. With the deduction of these 50 doubtful cases there are left only 84 that are definite. This number is much smaller than the expected incidence rate from the Baltimore City morbidity rates for similar groupings of women, and strongly points to the possibility that

there are a number of patients with pulmonary lesions which are overlooked in the obstetrical service.

2. PREGNANCY WITH DEFINITE BUT INACTIVE PULMONARY TUBERCULOSIS

We have 17 patients whose histories and signs pointed conclusively to the diagnosis of pulmonary tuberculosis in an inactive stage at the time of delivery. Ten of these patients showed unilateral, and 7 bilateral, localization of the disease. For the better study of these cases it is necessary to record abstracts of their histories.

Abstracts of cases

7634. White, 21, primipara. She had been followed in the Phipps tuberculosis clinic for 2½ years, where percussion changes at both apices were noted. Her case was regarded as inactive. She had an uneventful pregnancy and was delivered of a healthy baby, weighing 3650 grams. She continued well, and 4 years later became pregnant a second time. During the 5th month she had a severe haemoptysis, followed by a spontaneous abortion. One year later she was found to be in excellent condition, but with dulness and harsh breath sounds at both apices. No signs of activity.

9392. White, 42, multipara. 5 previous healthy children; oldest, 24, youngest, 12 years. Two years before she had been treated for definite bilateral tuberculosis, confirmed by an X-ray and manifested by percussion changes and tubular breath sounds (Phipps). One and a half years before pregnancy, she spent 6 months at the State Sanitarium. At the time of pregnancy, the lungs showed no activity. She ran an uneventful course and was delivered of a healthy baby, weighing 3120 grams. Four years later she was in good condition and showed no signs of activity.

5603. White, 22, primipara. Two years before her pregnancy the patient's brother died of tuberculosis. One year later she had an haemoptysis and was found to have definite percussion and breath sound changes at the left apex with râles (Phipps). She was sent to Eudowood Sanitarium for 4 months, where her physical signs became inactive. She became pregnant and continued well until 7 weeks before delivery, when she had a flare-up of her lung process. The sputum was negative, but there were signs of activity at the left apex. She was spontaneously delivered of a normal baby, weighing 3175 grams. The obstetrical ward discharge note says "Patient in no worse condition than on admission." No further record.

5900. White, 26, primipara. Cough, loss of weight and weakness. The examination disclosed impaired percussion in the upper chest with modified breath sounds with fine râles (Phipps). Her condition became inactive under

treatment. Seven years later she became pregnant, at which time her pulmonary condition was inactive. She had an uneventful pregnancy and was delivered of a healthy baby, weighing 2600 grams. Both mother and child were discharged in good condition. One year later she lost a little weight and some signs of activity were made out. She improved, but two years after this her weight again went down, and her lung process flared up, to be followed, after treatment, by a return to inactivity.

5926. White, 32, multipara; one spontaneous abortion and 5 healthy children; oldest 14 years, youngest 18 months old. One brother had died of tuberculosis. Four years before this pregnancy, following a five-month spontaneous abortion, a diagnosis was made of pulmonary tuberculosis of the right apex (Phipps). She did well and the signs of activity disappeared. The report of the present pregnancy is that she was delivered outside the hospital. No report of the baby is available. Four years after this she became pregnant again, with an uneventful course. At this time the lung process was quiescent, but seemed slightly more widespread than when first seen. The X-ray showed diffuse infiltration of both uppers. Five years later—nine years after her first baby and five years after the second—her condition was good and the lung showed only a healed lesion.

6026. White, 26, multipara. One spontaneous abortion at 4 months; 2 healthy children, 6 years and 18 months old. The patient thought she was well until 4 months before pregnancy, but at this time developed a cough and bloody sputum. She was seen one month later and was found to have definite signs at the right apex (Phipps). She improved and one year later was delivered spontaneously of a healthy baby, weighing 2650 grams. Two weeks later she was discharged in good condition. No further record.

6028. White, 31, multipara. Four previous normal pregnancies; oldest child 10 years, youngest 6 years. Five years before this pregnancy a diagnosis of pulmonary tuberculosis, involving the right apex, with dulness and râles had been made (Phipps). She did well, and had an uneventful pregnancy, with no signs of activity of the lung process. Her baby weighed 3830 grams. She was discharged in good condition. No further history.

4180. White, 35, multipara. Three healthy children, oldest, 10, youngest, 1 year old. The patient had been in the Phipps Clinic 10 months before pregnancy, with active tuberculosis of the upper left lung. She responded well to treatment and, when seen in the obstetrical dispensary, there were no signs of activity. Her pregnancy was uneventful and she was delivered of a healthy baby, weighing 3670 grams. Her lungs on discharge showed nothing beyond definite dulness and distant, modified breath sounds over the left upper. She had 3 subsequent normal pregnancies, and 5 years later the lung condition was unchanged. Six years after this she entered the municipal tuberculosis hospital, for treatment of a slowly, progressive pulmonary lesion.

4688. White, 26, multipara. One previous normal child, 3 years old. The patient's husband had tuberculosis. On the ward it was found that the right

upper showed impairment with harsh breath sounds and an occasional crackle. The left interscapular region showed similar signs. Her pregnancy was uneventful and her healthy baby weighed 2610 grams. She was discharged in good condition. When seen 6 months later in the Phipps Clinic, the physical signs were corroborated and the diagnosis was made of "quiescent pulmonary tuberculosis."

4741. White, 34, multipara. Five previous normal pregnancies; oldest child, 10 years, youngest, 20 months. On admission the patient showed percussion dulness and prolonged harsh breathing at both apices and both interscapular regions, with occasional râles. The X-ray showed an advanced lesion in the right and a slight lesion in the left chest. She had a spontaneous, 3 months' abortion, probably due to a myoma of the uterus, and was discharged with her lung signs unchanged. She subsequently went to a sanitarium for 22 months, and became much better. Three and a half years after the abortion, her physical condition was good, the lungs showed the same degree of involvement but there were no signs of activity.

4850. White, 34, multipara. Two previous spontaneous abortions and 3 healthy babies; oldest, 11 years, youngest, 3 years. The patient had been seen in the Phipps Clinic 2¼ years before, for an active lesion at the right apex. She did well, became pregnant and, after an uneventful course, gave birth to a healthy baby, weighing 3550 grams. While on the ward prolonged and harsh expiration, with dulness and an occasional râle at the right apex, were noted. She was discharged in good condition. For 4 years the process was quiescent, but then became active and she was sent to a sanitarium. Her X-ray showed fibrosis of both uppers at this time (Phipps). She did well and 2 years later the process seemed quiescent, but perhaps more extensive. Six years later she had haemoptyses, and the process seemed to be slowly advancing.

5019. White, 29, multipara. One previous healthy baby, 4 years old. The patient was found on the obstetrical ward to have impaired percussion, with tubular breathing and occasional râles at both uppers. Diagnosis "inactive pulmonary tuberculosis" (Phipps). Her pregnancy was uneventful, and she had a healthy baby weighing 3370 grams. She was discharged two weeks after delivery in good condition. No further record.

4886. White, 20, primipara. Her father had died, probably of pulmonary tuberculosis. Four years previously she had been seen in the Phipps Clinic for active tuberculosis, involving the right upper, with impaired percussion, harsh breath sounds, and moist râles. She went to a Sanitarium and her process became quiescent. At the time of pregnancy her lung signs were those of an inactive lesion of the right apex. Her course was uneventful and she gave birth to a healthy baby, weighing 3810 grams. On discharge 18 days after delivery she was in good condition. No further record.

4864. White, 32, multipara. In 1907 she had active tuberculosis involving both uppers but with extensive signs at the right apex (Phipps). She improved and the following year the signs of activity were less, but there was, on inspection,

considerable retraction that suggested fibrotic changes. In 1910, the same dulness and modified breathing were found, but no signs of activity, and she was in good general physical condition. She went through an uneventful pregnancy in 1911, 4 years after the first knowledge of tuberculosis, and 2 weeks prematurely gave birth to a baby that weighed 2080 grams. This mother and child were discharged in fair condition. No further record.

4635. Colored, 30, primipara. Her father, brother and husband had died with tuberculosis. At the time of her admission, she showed restricted expansion, impaired percussion and harsh breath sounds, with occasional râles at the left upper. The right apex showed definite but less extensive involvement. These findings were corroborated, but the lesion was regarded as inactive (Phipps). Her general condition was good. Pregnancy was uneventful and her healthy baby weighed 3100 grams. When seen 6 months later, she was in good condition, with no change in the lung findings.

2696. White, 21, multipara. Three previous normal pregnancies; oldest child 5, youngest 2½ years old. The patient had a tuberculous family history. In the Phipps Clinic 4 years before, a definite lesion was made out, but by the time she came to the obstetrical ward, the lungs were recorded as negative. She had an uneventful pregnancy, and her baby weighed 3035 grams. She was discharged in good condition. No further record.

10591. White, 33, multipara. Three previous spontaneous abortions, 4 normal babies, oldest 10, youngest 3 years. Six months before delivery, the patient's lungs were reported as clear. One month later, she had pleurisy with effusion and was admitted to the medical ward, where fluid with 160 lymphocytes per cubic centimeter was aspirated. Her condition improved, and 1 month before delivery, the only signs were of a thickened pleura on the left, with no definite pulmonary changes (Phipps). She had an uneventful delivery, with a baby weighing 3110 grams, and was discharged in good condition. One month after delivery, the only signs were those of a thickened pleura, and the X-ray showed only haziness in the left thorax. Six months later, she was admitted to the gynecological ward for a repair operation. The lungs were negative and the X-ray showed them to be clear.

To sum up these abstracts, one may say that they comprise 17 cases of clinically definite pulmonary tuberculosis, inactive at the time of delivery, for 10 of whom we have follow-up notes for 6 to 12 years after delivery. Of these 10, none had died. One patient had "flare-ups" 1 year and 2 years after delivery; 1 had 4 subsequent pregnancies within 5 years, during which time the lesion was quiescent, but 11 years later she went to a Sanitarium. One had a flare-up 4 years after delivery, necessitating treatment in a Sani-

tarium, but at the end of 6 years she was in good general condition, though the lesion seemed somewhat more advanced. On the other hand, 7 of the 10 patients were in excellent condition, from 6 months to 5 years after delivery. All but 2 of the 17 patients had normal full-term babies.

There are several points to be noted in regard to this group. In the first place, it is entirely made up of mothers without financial resources. Social service assistance was possible in only a small porportion, and then only for brief intervals and of small amount. These women had the household duties and the care of families to a greater or less extent, and belong to the class which, in general, is unfavorable for the care of tuberculosis. In spite of this fact, out of 10 patients whose after histories are known, 7 did very well. Again, the ordinary course of inactive tuberculosis in non-pregnant women women must be considered, since there is always a certain proportion of patients who have flare-ups in the course of their lives, regardless of the treatment. The histories of our patients who had recrudescences do not convince us that the pregnancy was to blame. Certainly, they were not more numerous than in non-pregnant women with inactive tuberculosis, and did not appear until a number of years after the pregnancy. It is much more likely that the wear and tear of their particular lives would have produced such "flare-ups" whether they had had babies or not. Another interesting feature is, that the length of time before pregnancy of the discovery of tuberculosis does not seem to influence the after result. If the pregnancy was the sole factor that modified the course of the tuberculosis, it would be fair to conclude that if the lesion had been quiescent for 3 years previously, the subsequent course would be more favorable than if activity had developed at the time of pregnancy. This is not borne out by our observations, for some of the patient whose lesions had been quiescent for the longest time had a recrudescence of symptoms a year or so after delivery, while several whose first intimation of pulmonary tuberculosis developed early in pregnancy, went through an uneventful delivery, provided the lesion became quiescent, and subsequently showed no flare-up. We believe that often pregnancy is coincidental and that pulmonary tuber-

culosis itself is a very individualizing disease. Once infected, a woman with a quiescent lesion has always the possibility of a flare-up, depending on the nature of her particular lesion, as well as upon her social status. Obviously, the longer the duration of inactivity, the less likely the possibility of recrudescence, because time is allowed for more complete fibrous walling off of the original lesion. Of 2 patients with clinically equal lesions, the one whose activity subsides, and who goes 3 or 4 years without a flare-up, has a better prospect than the one whose lesion is barely controlled and who has occasional recrudescences. On the other hand, we believe, and probably with the approval of those conducting tuberculosis Sanitaria, that it is never possible to give an absolute diagnosis of a cured pulmonary tuberculosis that will never break down. The general concept of pulmonary tuberculosis must be applied to the discussion of these obstetrical patients, and then perhaps it is not so evident that the pregnancy itself is the essential feature. Moreover, if pregnancy is as important as many writer simply, would not the majority of these inactive cases be made worse? And further, why is it that on a large obstetrical service, where there are undoubtedly many early cases that escape recognition and where there are many patients with repeated pregnancies, there is not a constant path travelled from the ward to the tuberculosis dispensary? Patients in one department are constantly referred to other departments, and patients who have been on one service and subsequently develop another disease generally go back to the same institution for treatment. It is rare for patients who have been in our obstetrical service to return to our medical or tuberculosis dispensaries for what turns out to be pulmonary tuberculosis, whereas it is common for patients who have been delivered on the outside or inside obstetrical services to come to medical or gastro-intestinal clinics for treatment for diseases other than tuberculosis. We appreciate the possibility of tuberculosis developing after delivery and after discharge from the wards, but we are unable to find more than 3 or 4 such cases, although it would be expected that, in such an event, a large proportion of the patients would be found later in our dispensary for treatment for tuberculosis.

3. PREGNANCY ASSOCIATED WITH ACTIVE TUBERCULOSIS

We were able to find 31 patients who had active tuberculosis during pregnancy and at the time of delivery, and their histories are abstracted.

Abstracts of cases

10270. White, 32, multipara. Seven previous pregnancies; only the youngest child is living, 2 years old, and he has tuberculous osteomyelitis. Her two husbands and a sister died with tuberculosis. Two years before delivery, she was found to have a thickened pleura on the right, with definite but not extreme tuberculous infiltration of the left upper lobe (Phipps). She did well under treatment, but came to the obstetrical ward with an acute condition manifested by haemoptysis, râles and positive sputum. The X-ray showed infiltration of both uppers. She had a normal obstetrical course with a baby that died six months later, of "diarrhoea." One year after delivery she still had an active process at the left upper, with no marked increase of her lesion. Four months later she was delivered of a second child, after an ordinary obstetrical course, and was in good condition 8 months later. Eight months later, her general condition was fair but there was definite activity, and the X-ray showed beginning cavitation. Cough and sputum were still present. She was working regularly.

9789. Colored, 34, multipara. Eight pregnancies; 6 children living and well, oldest 13, youngest 3 years. The lungs were reported clear at the time of the last delivery, on the outside obstetrical service. Six months before the present delivery, both uppers were dull with harsh breath sounds and râles. There were suggestive signs of cavitation at the right. The X-ray showed marked involvement of both lungs (Phipps). She had a normal baby at term, that died in 1 year of pneumonia. Our patient died 6 months after delivery.

9246. White, 23, multipara. Two children, aged 3, and 2 years. The patient had 2 children with tuberculosis. Three years before delivery the lungs were reported as clear, by the Medical Dispensary. One year before delivery she developed signs of activity and was sent to a Sanitarium for treatment, from which she came for delivery. On the ward she was found to have a definite active lesion of the left upper. She had a premature labor at 7 months and the child lived, but was in poor condition 2 months later. She went back to the Sanitarium, but died within 18 months.

8493. White, 29, multipara. Five pregnancies; 3 children living. First pregnancy 13 years, the last, 2 years previously. The patient had 2 children with tuberculosis. She had been under the supervision of the Board of Health for 9 years. One month before delivery she had a severe haemorrhage and on the ward her lungs showed definite activity. Her discharge note says that she was generally better than on admission, but that the lung process was still active. Her obstet-

rical course was not remarkable and her baby was discharged in good condition. No further record.

7990. White, 20, multipara. Four pregnancies; 4 children living and well; oldest 6, youngest 3 years. On admission there were signs of definite involvement of both uppers and with dulness and râles. The sputum was positive. She was discharged in poor condition 2 months after delivery. No further record. Her baby died 6 weeks after birth.

7370. White, 32, multipara. Four children; oldest 8, youngest 2 years. On admission the patient showed signs of tuberculosis in both uppers. Just after delivery she was diagnosed in the Phipps Clinic as having an acute exacerbation of an old lesion and was sent to a Sanitarium. Both mother and child were discharged from the obstetrical ward in poor condition. No further record.

2696. White, 21, multipara. Three children; oldest 5, youngest 2 years. The patient's mother died from tuberculosis. Pulmonary tuberculosis was diagnosed 1 month before delivery (Phipps). At this time she showed impaired percussion note and persistent fine râles over the left upper thorax. Pregnancy and labor were uneventful. The child was discharged in good condition, and the mother's lung condition was improved. Four and a half years after delivery, she was reported to be "in good health" (not examined).

7027. Colored, 23, multipara. Three children; oldest 4, youngest 2 years. (On a previous admission to the hospital obstetrical service the lungs had been reported clear.) A consultation in the tuberculosis clinic reported a definite old infiltration at both apices with signs of activity on the left. She was delivered of a normal baby at term by Caesarean section on account of a rachitic pelvis. She was discharged 1 month later in good condition. No further report.

7456. Colored, 36, multipara. Nine children; oldest 17 years, youngest 9 months. Three months before delivery, moderately advanced bilateral fibroid tuberculosis, with signs of activity (Phipps). Pregnancy and labor normal; discharged in good condition 3 weeks later. Frequent examinations in the next 2 years showed clearly active tuberculosis, with haemoptysis and a rather downhill course. Two and a half years after this, she was delivered of a stillborn child, on the outside obstetrical service; the lungs still showed activity, and during the puerperium, she had fever and night sweats. Following influenza a year later, an examination in the tuberculosis dispensary disclosed subacute bronchitis and active tuberculosis. One year later (four and a half years after the first recorded child) she was again pregnant and an examination in the tuberculosis dispensary disclosed chronic bronchitis but no further signs of tuberculosis, and the weight had improved. She had a normal baby at term. Three years later, the weight had increased and the lungs were clear except for signs of chronic bronchitis.

9311. White, 21, multipara. Two children; 2 miscarriages. One aunt had died of pulmonary tuberculosis. Two and a half years before the present pregnancy, she had what was regarded as a case of moderately advanced bilateral tuberculosis, with no moisture. Seven months before delivery, the process was

definitely active with positive sputum. She entered a Sanitarium for 3 months. Two weeks after delivery at this hospital the child was in good condition, but the mother's process was active. Fourteen months after delivery, the process had advanced slightly and was clearly active. She entered a Sanitarium for 2 months, and her course seemed to be down-hill.

1008. Colored, 22, primipara. Shortly after admission, she had a spontaneous abortion at 6 months. While in the hospital, impairment of percussion and râles developed at both apices and spread gradually. Two weeks after admission, the sputum was positive. She was transferred to Bay View and treated there on two occasions, for brief intervals, but died about 1 year after her pregnancy.

10687. Colored, 35, multipara. Miscarriage at 3 months 18 years, and at 5 months 1 year previously. The patient's father had died of tuberculosis. At the time of the miscarriage, 1 year before, the lungs were reported normal. Following influenza 8 months before delivery, a persistent cough developed. A physical examination 6 months later disclosed the signs of active pulmonary tuberculosis on both sides. The sputum was positive and early cavitation at both apices was shown by the X-ray. She had an uneventful obstetrical history with a normal baby. Two weeks after delivery, she was discharged in better condition than on admission, but with some signs of activity. One year after discharge, she died. The child was in good condition.

10320. White, 20, multipara. Two children, 3 years old (dead), and 1 year. At the birth of the first child, the lungs were normal. After the second child she had an attack of pleurisy. Four months before the present delivery, she had a cough of 1 month's duration, but the lungs were negative on examination. At the time of delivery there was some impairment at the apices with modified breath sounds. Early in the puerperium, her cough increased, fever, night sweats and weakness developed, and the lungs showed many râles. She was discharged 1 month after delivery in poor condition. The child was quite normal. The mother died 8 months later, in the Municipal Hospital.

5735. Colored, 21, multipara. One child, 3 years old (dead). A brother had died with tuberculosis 8 years previously. Fourteen months before delivery, a physical examination in the tuberculosis dispensary showed impairment and râles at both apices and she gave a history of blood-streaked sputum. The signs of activity decreased until 3 months before delivery, when she had a slight pulmonary haemorrhage. She was treated at the Municipal Hospital and subsequently admitted to our obstetrical ward. She was discharged 2 weeks after delivery. The child was in good condition. One year later the general condition of the mother was worse and the process was still active.

6351. White, 31, multipara. Five pregnancies; oldest child 7, youngest 2 years. At the time of delivery the physical examination disclosed impairment with modified breath sounds and râles, and she was regarded as having an active pulmonary tuberculosis with pleurisy (Phipps). The puerperium was afebrile and the patient left the hospital 2 weeks after delivery, against advice, in poor

condition. Three years later the lung process was still active and the patient was at the State Sanitarium.

6553. Colored, 18, primipara. Six weeks before delivery impairment with marked changes in breath sounds over the left upper. Two weeks after delivery moisture developed throughout the left lung, and her sputum became positive. She was discharged 3 weeks after delivery in worse condition than on admission. No further report.

4412. White, 35, multipara. Three pregnancies; oldest child 9, youngest 3 years. The patient entered the hospital having had a spontaneous abortion at 4 months, with considerable haemorrhage. Examination showed both apices impaired with modified breath sounds and râles over the left upper. A diagnosis of active tuberculosis was made (Phipps). She was discharged 2 weeks later, with her pulmonary condition unchanged. Five years later, after she had lived in very poor surroundings, and had worked steadily, the pulmonary process was found much advanced and active. Eighteen months later, after 6 months in a Sanitarium, the process was still active and further advanced, and her general condition was very poor.

4783. Colored, 24, multipara. Two pregnancies; 1 child had died 6 years before, premature labor, 4 years before. A sister and brother had died within the year from tuberculosis. Symptoms of cough, nervousness and weakness began 3 months before delivery. Examination showed active tuberculosis at the left apex. She was discharged 2 weeks after delivery, in fair general condition. The child was normal. Three years later, examination showed moderately advanced lesions at both apices with a history of recent haemoptysis. Her general condition was worse.

3884. White, 35, multipara. One child, 2 years old (dead). The patient's mother had died of "lung trouble." The right upper lobe showed active tuberculosis. Examination by a laryngologist showed a tuberculous ulcer of the larynx. She was discharged 2 weeks after delivery in fair condition. No further record. The child was normal.

3546. White, 24, primipara. Admitted late in the second stage of labor. The lungs immediately after delivery showed nothing abnormal. Four days after delivery, pleurisy developed in the right upper chest. Five days later there was definite impairment with râles and positive sputum. Upon discharge, 3 months after delivery, the mother's condition was very poor, with marked activity of the process. The child was in fair condition. No further record.

3528. White, 39, multipara. Three children; oldest 14, youngest 6 years. On admission her right upper chest showed retraction, impairment, modified breath sounds and râles. She had had a cough and expectoration for more than a year. The sputum was persistently negative. She was discharged 2 weeks after delivery in fair condition. The child was normal. Five years later, an examination in the tuberculosis clinic showed some advance, with activity at both apices.

3144. White, 33, multipara. Three children; oldest 7, youngest 2 years. The patient had had weakness, cough and blood-tinged sputum for 2 or 3 years.

Both apices were impaired with tubular breath sounds and râles, and the sputum was positive. She left the hospital 3 weeks after delivery in poor condition. The child was normal. No further record.

3134. White, 38, multipara. Four children; oldest 10, youngest 4 years. The first symptoms of illness began 2 months before delivery with weakness, dyspnoea and haemoptysis. The left upper chest was retracted and impaired, and râles were present. The sputum was positive. She left the hospital 3 weeks after delivery in poor condition. The child was normal. No further record.

3019. Colored, 29, multipara. Three children; oldest 8, youngest 2 years. On admission she was found to have impairment at the left apex and base, with suppressed breath sounds, but no râles. In the tuberculosis clinic the diagnosis was made of an active tuberculous pleurisy with a healed lesion at the left apex. She was discharged 3 weeks after delivery in fair condition. The child was normal. No further record.

2893. Colored, 25, multipara. Three children; oldest 6, youngest 2 years. She was delivered 4 days before admission by the outside obstetrical service. When about 6 months pregnant, she had contracted a "cold" with a cough, sputum and night sweats. Physical examination disclosed impairment at the left apex and râles at both apices. The sputum was positive. She was discharged 3 weeks later in poor condition and died 1 month later. The child was in good condition at that time.

2521. White, 26, primipara. Admitted to the hospital because of postpartum haemorrhage, from cervical and vaginal lacerations. The child had died during a prolonged labor. The lungs were clear on admission. Impairment, râles and modified breath sounds over the left upper and right lower were noted 2 weeks after admission. The sputum was positive at this time. She was discharged in very poor condition 6 weeks after admission. No further record.

514. White, 45, multipara. Seven children. Cough, weakness and night sweats for 3 months before delivery. On examination, impairment, modified breath sounds and râles over the right upper. She was discharged 2 weeks after delivery in fair condition. The child seemed normal. A physical examination 12 years later showed extensive impairment with râles over the right and impairment at the left apex. Fifteen years after delivery, definite cavitation was found on the right, with activity; but her general condition was fairly good.

239. White, 31, multipara. Four children; oldest 8, youngest 2 years. A cough began 4 months before delivery. Physical examination on the ward disclosed scoliosis from lumbar spinal disease, impairment and râles throughout both sides and deficient expansion. Her sputum was positive and she had tuberculous ulceration of the larynx. The mother died 1 month after delivery. The child was in excellent condition at that time.

8661. O. O. S. Colored, 32, multipara. One child, 2 years old. An operation was done 8 months before confinement for tuberculosis of the kidney and breast. One month later she came to the hospital for chronic tuberculous nephritis. Her child was born prematurely at 7 months and died within 12 hours. Examination

of the mother at this time disclosed diffuse involvement with râles throughout both lungs. The abdomen showed distension and fluid, which suggested tuberculous peritonitis. The patient died 5 days after delivery.

1849. Colored, 17, primipara. The child was premature, weighing 1200 grams. It died shortly after birth. Physical examination of the mother disclosed impaired note at the left front, with râles and modified breath sounds throughout the left side. Her sputum was positive. Signs of cavitation developed shortly after delivery. She grew rapidly weaker, and died at a municipal hospital 3 months after delivery.

5516. Colored, 17, multipara. One child, 2 years (dead). She had grown markedly weaker in the last month. On examination, impairment at the left apex with râles and modified breath sounds throughout. Following delivery the lung signs became rapidly worse, and the sputum became positive. She died 11 days after delivery. Autopsy showed cavitation and miliary tuberculosis of the lungs. The child was premature but was discharged in good condition 63 days later.

With one exception in which there was a rachitic pelvis, these patients were not subjected to operative delivery. There were 4 spontaneous premature births and 2 deaths, and 2 spontaneous abortions at 6 and 4 months. So that 23 babies were discharged at the end of 2 weeks in fair condition. Their average birth weight was 2808 grams, which is definitely below the average for the service and is 400 grams below the average weight of the babies whose mothers had quiescent tuberculous lesions.

An effort was made to discuss the fate of the mothers from the point of view of the degree of the tuberculous lesion, but it is quite impossible to subdivide them satisfactorily and it really is of little importance. Suffice it to say that there are 11 whose histories are of too short duration to be worth while considering and that of the remaining 20, 2 (10 per cent) were improved, 8 (40 per cent) were unimproved, and 10 (50 per cent) were dead 1 year after delivery. This statement is more than fair, inasmuch as most of these patients were followed from 1 to 15 years after delivery, and their condition at the end of the known period is given as if for the end of 1 year.

It is interesting to compare these results with those obtained from a number of consecutive cases of actively tuberculous non-pregnant women obtained in the Phipps tuberculosis clinic at the end of a year.

	NUMBER OF CASES	LIVING AND IMPROVED		LIVING, NOT IMPROVED		DEAD	
		Number	Per cent	Number	Per cent	Number	Per cent
Non-pregnant	72	25	35	24	33	23	32
Pregnant	20	2	10	8	40	10	50

These figures are very small, but they show a definitely unfavorable prognosis for the pregnant woman. However, in studying the abstracts, it is seen that the higher mortality rate is due to the fact that where there is a far advanced or an acute rapidly spreading tuberculosis, pregnancy serves as the final straw and practically assures a lethal outcome. In other words, in our patients, we find that an active tuberculosis, except in the third stage of severity, has been followed by about a 10 per cent worse outcome than that to be found in non-pregnant women.

We would not like it to be assumed that in any way we favor pregnancy in the presence of active tuberculosis; for it should be most definitely stated that in our series, as has been found by most investigators, pregnancy was disastrous. The results of statistics and the pathological finding of fresh seeding in the lungs are all too conclusive for but one interpretation. When it is seen that in the presence of active tuberculosis pregnancy is followed by death in fully one-half of the mothers within 1 year, the dangers are evident. On the other hand, there are, clinically, two types of tuberculosis—the rapidly advancing active type in which the patient steadily goes downhill despite the most rigorous therapy, and the slowly advancing fibroid type which the patient, unaided, practically holds in check and which is most amenable to therapy. Obviously, then, the outcome can be roughly foretold and such a prognosis can be confirmed by histories. In the pregnant woman with a fibroid lesion for whom the most suitable therapy is available, the future is the best, while in the caseous lesion, with no anti-tuberculosis therapy, the outcome is fatal. Between these extremes there are various results depending on the type of lesion and the care of the patient, and these are exemplified in our series. But even in the patients who did not die, pregnancy was deleterious to the pulmonary condition.

4. PREGNANCY ASSOCIATED WITH TUBERCULOSIS IN WHICH A THERAPEUTIC ABORTION WAS DONE

A. Active tuberculosis with therapeutic abortion

Abstracts of cases

10290. White, 19, primipara. Cough 6 months before admission and 3 haemoptyses 2 months before the operation. On admission both uppers were impaired and the breath sounds were harsh and accompanied by many râles. The X-ray showed tuberculosis with miliary distribution. Hysterectomy was performed at the 3rd month. She left 3 weeks after the operation, in poor condition and died 5 weeks later.

11899. White, 24, multipara. Four children; oldest 6, youngest 1 year. The patient's mother and father had died with tuberculosis and her brother was suffering from the disease. An examination in the tuberculosis dispensary before the operation showed marked impairment over both uppers with many râles. The X-ray showed a large cavity on the left. Hysterectomy was done at the 3rd month. She was transferred 3 weeks later in fair condition to the State Sanitarium, but died in 12 months at the Municipal Hospital.

7351. White, 32, multipara. One miscarriage, 9 years ago; 3 children; oldest 8, youngest 1½ years. At the time of her admission, her brother, sister and mother had tuberculosis. Examination in the tuberculosis dispensary, 3 months before the operation, showed both uppers impaired with modified breath sounds and râles over these areas. Bilateral advanced tuberculosis was diagnosed. Her history showed rapid loss of strength with haemoptysis during the previous month. An abortion was performed at the 2nd month, after she had been in a State Sanitarium 5 weeks. She was discharged after 1 week and died 2 months later.

6676. White, 26, multipara. Two children; oldest 3, youngest 2 years. The patient's mother and two aunts had died with tuberculosis and a brother was suffering from it. Examination in the tuberculosis dispensary 6 years before operation showed impairment at both apices with a few râles at the right apex. The process advanced during the ensuing 5 years. One year before the abortion it was extensive on both sides and the sputum was positive. An abortion was performed at the 3rd month. The patient then entered the State Sanitarium but died 17 months after the operation.

6808. White, 28, primipara. Three weeks before the operation examination showed retraction, impairment, modified breath sounds and râles at the right upper. The diagnosis was made of an extensive fibroid lesion with a small active focus. The sputum was positive. An abortion was done at the 3rd month. She was discharged 2 weeks later in good condition. No further report.

6858. White, 25, multipara. Three children; oldest 5, youngest 2 years. The patient's father had died with tuberculosis. Her condition was diagnosed as inactive fibroid tuberculosis, in the tuberculosis dispensary, 5 years before the present pregnancy. During pregnancy 3 years before operation, the lungs were

inactive, but when she was pregnant again 1 year later, the process had advanced considerably and showed definite activity. When admitted for the present pregnancy, the physical examination disclosed râles and modified breath sounds over both uppers, with consolidation and evidence of cavitation at the right apex. Her sputum was positive. Hysterectomy was performed at the 2nd month. Two weeks after the operation, she was discharged in poor condition. She improved somewhat after a year at the State Sanitarium. Four years after the operation her general condition was poor; the process was still active with occasional haemoptyses.

7283. White, 29, multipara. One miscarriage, 2 years previously; 2 children, oldest 9, youngest 5 years. She had spent 6 months in a sanitarium before her admission to the ward. She had had tuberculosis of the lungs for about 1 year. Physical examination showed impairment over both uppers, bordering on flatness at the right apex, with râles at both apices. She was submitted to a salpingectomy when 6 weeks pregnant, and discharged in good condition. Her general condition remained fair, although the process in the lungs showed constant activity of a low grade during the ensuing 4 years. She was at a sanitarium on three occasions during this time.

7489. White, 31, multipara. Four children; oldest 9, youngest 2 years. Her husband and 1 child had tuberculosis. Four years before the present pregnancy, she showed active tuberculosis, with impairment, modified breath sounds and many fine râles over both uppers (Phipps). She was at the State Sanitarium for 3 months. Eight months before operation, the area of impairment and râles had extended considerably and the process was active. Abdominal hysterectomy was done at the 3rd month. Five months later, the patient was in good condition, except for an old fibrosis at both uppers.

4144. White, 29, multipara. Two miscarriages; 2 children; oldest 8, youngest 4 years. Two brothers had died and one was sick with tuberculosis. The patient had had a cough and loss of weight for 1 year. Eight months before the operation "early pulmonary tuberculosis" was diagnosed (Phipps). The left apex was impaired, with harsh breath sounds and many râles. The sputum was positive. The uterus was emptied and the patient was discharged in good condition 2 weeks later. No further record.

4394. Colored, 36, multipara. One miscarriage; 5 children; oldest 10, youngest 2 years. Six months before the operation the patient began to cough and lose weight. A physical examination showed limited movement, impairment, harsh breath sounds and râles at the right apex. A diagnosis of active tuberculosis was made. An abortion was done at the 2nd month. She was discharged 2 weeks after the operation in good condition. No further record.

7682. White, 41, multipara. Two miscarriages; oldest 20, youngest 10 years. The patient's mother and brother had died with tuberculosis. The patient had had a chronic cough for 20 years. She was known to have had clinically active tuberculosis for 2 years (Phipps)—impairment at both apices with tubular breathing and râles over the right upper. Hysterectomy was performed at the 3rd

month. She was discharged in good condition but rapidly grew worse. Four months after the operation, her sputum was positive and signs of consolidation had appeared at the right apex. Twenty months after the operation the patient died.

3132. White, 24, multipara. Two children; oldest 5, youngest 3 years. The patient's husband and one child had died with tuberculosis. When examined 3 years previously, the right apex showed impairment, modified breath sounds and râles; a tuberculous lesion was diagnosed (Phipps). When seen at the time of the present pregnancy, the right apex showed little change and the process was apparently inactive there, but the left showed impairment with many râles. An abortion was performed at the 6th month. She was discharged in good condition, 10 days after the operation. During the ensuing 5 years, the patient did very well. A physical examination 10 years after the operation showed an acute flare-up, from which she recovered. The last examination 16 years after the operation showed the patient to be in good condition, and the X-ray showed her lungs to be clear except for an old fibrosis at both uppers.

All of the abortions were done between the 2nd and 3rd months of pregnancy, except 1 at the 6th month. There are 12 such patients of whom 3 could be followed for only 2 weeks after operation and so are discarded. Of the remaining 9 patients, 2 (22 per cent) were living and improved at the end of 1 year, 2 (22 per cent) were living but not improved at the end of 1 year, and 5 (57 per cent) were dead within 1 year. This is a small group, but we feel that the figures are more than suggestive when compared with the similar group in whom abortion was not done, for it suggests that the prognosis is made worse by operation. And, of course, the baby is sacrificed.

We feel that this is an important observation and merits careful investigation. If it is substantiated, as we believe it will be, then operative procedures will be discontinued in pregnancy complicated by active pulmonary tuberculosis. On the other hand, it is conceivable that evacuation of the uterus early in pregnancy, may be brought about under spinal anaesthesia, without shock to the patient, or at least, with a degree of shock which is counterbalanced by the protection of the patient against the unfavorable result of going to term. However, with the technique in vogue today, we feel that operative procedure in the presence of an active pulmonary lesion is followed by a higher mortality rate than if expectant therapy alone is employed.

There are 7 other patients with inactive tuberculosis, upon whom

a therapeutic abortion was done, and whose subsequent history is known. All of them were doing well at the end of 1 year, which is approximately the result found in the inactive patients who were allowed to go to term. Their histories are abstracted and included.

B. Inactive tuberculosis with therapeutic abortion

Abstracts of cases

12286. White, 24, multipara. One miscarriage 2 years before, 3 children, oldest 7, youngest 3 years. Active tuberculosis 1 year before the first pregnancy (Phipps). She was treated in the State Sanitarium. At the time of the first pregnancy, the lungs were inactive and her condition excellent. The condition was still inactive at the time of the second pregnancy 2 years later. In the third pregnancy, some moisture was found at the left apex, but her condition was good, when examined 1 year later. During the last pregnancy, the X-ray showed inactive fibroid lesions at both apices. A hysterectomy was performed at the 3rd month of pregnancy. One year later, her condition was good and the tuberculosis was inactive.

4527. White, 20, primipara. The patient's father had died with tuberculosis. Retraction, impairment, and modified breath sounds at the left apex, but no râles heard. The diagnosis was made of moderately advanced, inactive tuberculosis (Phipps). An abortion was performed at the 3rd month and she spent 3 months at a sanitarium. Six years later the lungs were still inactive, although the patient complained of loss of weight and weakness. No further record.

5622. White, 30, multipara. One miscarriage 11 years before; 5 children, oldest 10, youngest 1 year. One sister had tuberculosis. Five months before operation she developed a cold, lost weight and had some haemoptysis. At the time of her operation, there were modified breath sounds, impairment and a few mucous râles over both uppers. An abortion was performed at the 3rd month. She was discharged in good condition 10 days later. No further record.

2461. White, 29, multipara. One miscarriage at 7 months. Her father had died with tuberculosis. She had been treated during the past year in the Phipps Dispensary, and when 3 months pregnant, the tuberculosis was inactive. However, an abortion was performed. She was discharged in good condition 10 days later. No further record.

2924. White, 28, multipara. One miscarriage 3 years previously; 1 child, 2 years old. Cough and blood-streaked sputum for 3 years. Observation during the past 3 months showed impairment, modified breath sounds and a few râles at both apices (Phipps). Condition good. An abortion was performed at the 6th month to allow her to accept an opportunity to go to a favorable climate in the West. She was discharged in 2 weeks in good condition. No further record.

3229. White, 43, multipara. One miscarriage 6 years previously; 3 children; oldest 19, youngest 4 years. The patient's mother had died with tuberculosis

after being nursed by the patient. Two of the children had chronic tuberculous bone disease. Cough, weakness and expectoration began 10 months before the present pregnancy. Examination in the Phipps Clinic showed impairment, modified breath sounds and an occasional crackle at both apices and over the right upper. An abortion was performed at 2½ months. Six months later the lungs were inactive, the signs in general unchanged. The patient felt well.

4467. White, 34, multipara. Two miscarriages, 9 years and 2 years previously; 9 children; oldest, 11 years, youngest, 6 months. She had been treated for 18 months previously in the Phipps Clinic and showed diminished expansion and resonance with modified breath sounds on the right upper with an occasional click at both apices. The diagnosis was made of a moderately advanced inactive lesion. An abortion was done at 2½ months. Frequent observation during the following 2 years showed no advance in the process. The lungs showed no activity. Tuberculin had been administered during this time. A note was made that the patient had refused an abortion during the preceding pregnancy, although her tuberculous condition was known.

5. PREGNANCY ASSOCIATED WITH TUBERCULOSIS AND SOME OTHER DISEASE

The final group of our patients comprises those who besides tuberculosis had another disease during pregnancy. There are 19 such cases. Of these the syphilis group is shown and the other cases are summarized.

Tuberculosis complicated by syphilis

	NUMBER OF CASES	MOTHER LIVING AFTER 1 YEAR	MOTHER DEAD AFTER 1 YEAR	CHILDREN STILLBORN	DEAD AFTER 3 MONTHS	LIVING 3 MONTHS LATER
Inactive	5	5		5		
Active	5	1	4	3	1	1

Chronic nephritis (3 cases). Two patients with active pulmonary tuberculosis and one with an inactive condition—all died within one week after delivery.

Two children stillborn, one died in three days.

Cardiac disease. Mitral insufficiency and inactive tuberculosis—patients living and well one year later.

Malignant endocarditis and inactive tuberculosis—death *intra partum.*

Fatty heart and inactive tuberculosis—death *intra partum.*

Myocardial weakness and inactive tuberculosis—patient living and well one year later.

Eclampsia. One with inactive tuberculosis and one with slightly active—both patients living and well one year later.

Chloroform necrosis of the liver and active tuberculosis. The mother died four days after delivery.

Postpartum septicemia and active tuberculosis. Mother living but in very poor condition, three months later.

In this total group it is evident that in the presence of active tuberculosis and another disease the prognosis is uniformly bad and that, if the tuberculosis is inactive, the general result depends on the severity of the concomitant disease.

In summing up this present report we would like again to express our recognition of the fact that we are dealing with small numbers of patients in the different groups. But it is very difficult to get satisfactory material and the need for a larger number from this and other hospitals is evident and will be forthcoming, provided the records include careful follow-up notes.

With this investigation at its present stage we would like to discuss further the present results especially with regard to the variety of opinions that have been expressed as to the significance of pregnancy associated with tuberculosis. And again we must call attention to the importance of the social status of our patients. The majority of our patients had to work, but their physical capacity was curtailed by pregnancy. So that, in a way, in some of them, pregnancy served as a means of enforcement of rest—the therapeutic procedure for tuberculosis. On the other hand, with some of the mothers, pregnancy meant the same amount of work plus the physical burden of carrying and nourishing the foetus. But even in this group there was necessitated some rest in the latter months of pregnancy and during the early puerperium. Moreover, in many instances, the attention of the patients was directed to their tuberculosis, for which they were sent to the Phipps tuberculosis dispensary, en route to a sanitarium whenever the social service department could control their home conditions. Moreover, a definite percentage of these patients would have died, no matter what the treatment and no matter whether or not they had become pregnant. In other words, pregnancy represents additional work in some, while in others it represents a decrease in physical work, and the plus or minus results depend greatly on the individual life. It is the algebraic sum-

mation of work and rest in the individual's daily life that, beside the particular type of lesion, seems to us to control the prognosis.

In regard to the treatment of tuberculosis, we feel that every person so afflicted needs protracted rest in bed. But even if such treatment were possible in every case, there would always be a definite percentage of patients whose lesions are so overwhelming or in whom the resistance is so low, that they would die. We agree with Bernard who says "It is better where one is tuberculous to not become pregnant," and we feel that the risks of pregnancy are definitely increased by tuberculosis, depending, to some degree, on the type of lesion. But this risk is by no means prohibitive in inactive cases, provided that the household duties can be controlled, additional rest obtained, and the lesion is of the fibroid type and has been quiescent for at least 3 years; so that, where there is an overwhelming desire for children, the risks of pregnancy may be assumed. Cleisz expresses our opinion when he says that "in general it is less a statistical study of lesions than their dynamic study."

If we have made clear our general conception of the relationship between tuberculosis and pregnancy, the next problem is: What shall we do in the case of a pregnant woman in whom active tuberculosis is found. And here we have no hesitancy in our advice. Treat the tuberculosis to the uttermost, and disregard the pregnancy. Rest and more rest, preferably in a sanitarium, and under those whose life's business is the treatment of tuberculosis. *Artificial termination of pregnancy is not indicated*, and in our series, has led to a somewhat worse outcome. The excitement, the etherization, the shock of the operation, are additional factors that curtail the patient's strength just at the time when every bit of resistance is most needed to combat the acute onset, or the "flare-up" of the tuberculous lesion. Common sense would decry such generalship that depleted an attacking force! Hence, we cannot agree with Norris, Pankow and Kuyferle, Kehrer, Bar, Sergent and the host of writers who advise the termination of pregnancy in the early stages in the presence of tuberculosis, for we believe that at no stage of pregnancy is operation warranted.

On the other hand, we feel that a later sterilization is an entirely different matter—to be done at some period after the patient has

been through her pregnancy, and the tuberculosis has become quiescent. It is obviously not right to allow a tuberculous mother to be subjected to repeated pregnancies with repeated recrudescences of an old lesion. The use of tubal sterilization seems, in general, to be the most satisfactory procedure, but even such operative measures should be adopted only after a consultation between obstetrician and practitioner, and then only if they agree that in the individual patient future pregnancies are contra-indicated.

The next important problem in this connection is the child. Here, one can make fairly definite statements. The child of the mother with active tuberculosis has a poor chance of escaping infection, and when it is in constant association with the mother, the figures from our own observation and from various writers show a mortality of over 50 per cent within the first year. And even if they live, the incidence rate of tuberculosis is very high, for, inasmuch as children in the first 2 or 3 years of life are remarkably susceptible to tuberculosis infection, the intimate contact between mother and young baby tends nearly always toward the infection of the child. The custom of this clinic is to take the babies at once on birth and provide wet nurses or artificial feeding and, when possible, subsequent institutional care. Armand-Delille shows that among 787 children in 175 tuberculous families, 323 placed in the country away from their mothers were all well, whereas, of 396 children not so provided for, 238 developed tuberculosis. So we feel that if there is any sign of activity in the mother, the child should be taken away and brought up elsewhere, until her death, or until her lesion has become quiescent. Furthermore, the extra work of nursing the baby is obviously harmful to the mother, and even in quiescent tuberculosis, it is probably safer to advise as short a nursing period as is compatible with the fair interest of the child.

The question of an allergic state in pregnant women with tuberculosis is interesting, but the work to substantiate it is not yet conclusive. The recent papers by Cleisz, Bar, Devraigne, Nobecourt and Paraf develop contradictory conceptions that will serve us as the basis of experimental work to be undertaken the coming year. But even with definite conclusions obtained, it seems to us that the results to be worth while must be coördinated with the latter histories

of patients. And always one is confronted with the obstetrical condition of the patient and the many factors that enter into the result, besides the pulmonary disease. Each patient is a problem and it would seem that, in the solution of the problem, we again recognize that difficult procedure in medicine—before trying surgical therapy we must be sure that medical treatment will not avail.

We wish to express our gratitude to Professor J. Whitridge Williams for privileges accorded and for his kindly interest in this work.

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OBSERVATIONS ON THE EFFECTS OF LIVER EXTRACTS IN HYPERTENSION PRODUCED BY GUANIDINE COMPOUNDS

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In a former communication attention was called to the marked effects of liver extracts upon the hypertension produced by the injection of guanidine compounds (1). Since the depressor action is so striking in this experimental hypertension and also in patients suffering from arterial hypertension (2), a further study of this liver extract was undertaken.

The depressor action of various tissue extracts upon normal blood pressure has been known for many years. Oliver and Schäfer (3), in 1895, found that aqueous and glycerine extracts of the thyroid gland, spleen, parotid and submaxillary gland, when injected intravenously, produced a fall in blood pressure. Von Fürth and Schwarz (5), in repeating the experiments of Oliver and Schäfer, came to the conclusion that the effect of thyroid extracts in lowering the blood pressure was due to choline. The work of Vincent (6), however, indicates that their conclusions were probably erroneous. Popielski (4), in 1911, isolated from various organs, including the thymus, intestine and brain, a substance he named "vasodilatin," which produces a fall in blood pressure and which he stated was neither choline nor peptone.

Fawcett, Rogers, Rahe and Beebe (7), studying the effect of thyroid extracts upon the blood pressure, described a "residue" which has a marked depressor effect when injected intravenously, but which is inactive following subcutaneous injection. They noted also that the active portion of the "residue" is soluble in alcohol, is not precipitated by basic lead acetate and is not altered by boiling or passage through a Berkefeld filter. Its activity also apparently bears no relation to its nitrogen or iodine content when compared with other fractions obtained from the thyroid gland.

Abel and Kubota (8), in an extensive study of the depressor effect of various tissue extracts, including that of the liver, attribute this action to histamine. They also state that histamine is the toxic constituent of Witte's peptone, a substance which produces on injection a fatal lowering of blood pressure, that it is a widely distributed constituent of all animal tissues, is present in pure casein and is probably the active principle of Popielski's "vasodilatin." Their conclusions, however, are not entirely accepted by Hanke and Koessler (9, 10), who found no histamine in the perfectly fresh pituitary gland, in the liver of two normal guinea-pigs or in the liver of a man who had died of an accident.

Roger (11, 12) has recently studied the effects of various tissue extracts, especially those of the liver. He found substances that produce both a lowering and an elevation of blood pressure and states that the latter substance is soluble in alcohol and passes through a dialysing membrane.

From this very brief review of the action of various tissue extracts upon the blood pressure, it is seen that the depressor effect has been atrributed by some to three substances, choline, histamine and peptone.

Modrakowski (13), in 1908, stated that pure choline produced, on injection, a rise in blood pressure instead of a fall, and that the depressor effects previously described were due to an impurity. Mendel, Underhill and Renshaw (14) were unable to confirm his results and their work, as well as that of others, seems to establish beyond doubt that choline has a depressant action upon the circulation. Whether, however, it is the active depressant substance in the various tissue extracts studied is doubtful.

There seems to be no doubt that histamine has a powerful depressant action upon the arterial pressure; but that it is the active depressant substance in certain tissue extracts and proteins is not so well established. The most widely used tests for histamine are based upon its two striking biological characteristics—an ability to produce marked contractions of the virgin guinea-pig uterus and the marked fall in blood pressure following intravenous injections. Hanke and Koessler (15) have shown, however, that a histamine-free fibrin peptone may

cause contraction of the excised virgin guinea-pig uterus and may also produce a profound fall in blood pressure.

The marked fall in blood pressure which results from intravenous injection of peptone has been the subject of much study since the original experiments of Schmidt-Mülheim, in 1880. Abel and Kubota (*l.c.*) found histamine to be present in Witte's peptone and ascribe the depressor effect of peptone to histamine. Hanke and Koessler (15), however, as stated above, have described a histamine-free peptone that can cause a lowering of blood pressure.

In the course of our work with the liver extracts it was obviously of fundamental importance to determine whether the depressor effects were due to choline, histamine or peptone. This problem was investigated from several different angles and a brief report of this work is presented in this paper.

METHOD OF PREPARATION

We have found that a depressor substance can be extracted from the liver by a variety of methods. It can be extracted either by acidified alcoholic solutions or by acidified aqueous solutions, the latter withstanding boiling for three hours without loss of their depressor activity. The method of preparation employed most frequently was that of alcoholic fractionation.

A liver mash made with equal parts of freshly ground liver and alcohol acidified to 2 per cent with sulphuric acid was first prepared, the alcoholic content of the whole being 50 per cent. The filtrate from this mixture was obtained and the alcoholic content increased through successive stages. Each increase in alcohol produced precipitates which were discarded until a strength of 92 per cent alcoholic solution was reached, when the precipitate was saved and the filtrate discarded. This precipitate was dissolved in distilled water acidified to Ph. 2, treated with absolute alcohol and shaken with ether and chloroform. Further additional treatment of this liver fraction before various tests will be described later. This liver extract was found to exert a very marked effect upon the hypertension produced by guanidine compounds, but had no effect or at most only a slight transitory effect upon the normal blood pressure of the dog. It was most rapidly effective when injected intravenously, but also produced an effect

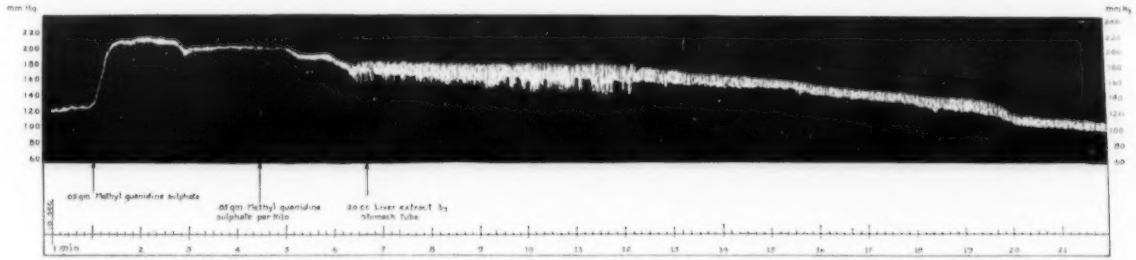

FIG. 1. FALL IN BLOOD PRESSURE PRODUCED BY LIVER EXTRACT ADMINISTERED THROUGH THE STOMACH TUBE

Blood pressure elevation produced by intravenous injections of methyl guanidine sulphate

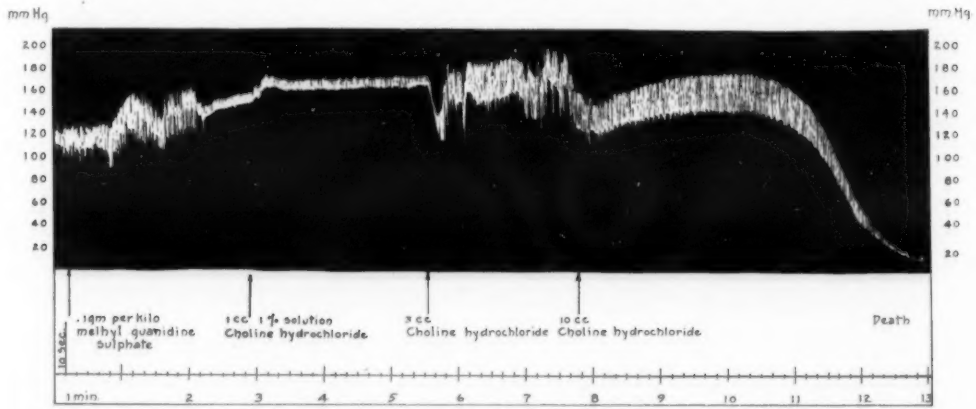

FIG. 2. EFFECT OF CHOLINE HYDROCHLORIDE UPON HYPERTENSION PRODUCED BY METHYL GUANIDINE SULPHATE

Injections intravenous

when injected subcutaneously or when administered through a stomach tube (Fig. 1).

Is the action of this extract due to choline? We have found, in agreement with the work of Mendel, Underhill and Renshaw (*l.c.*) that small doses of choline hydrochloride (varying from 0.5 mg. to 0.2 mg. per kilo of body-weight) will produce a transient fall in blood pressure. In dogs whose blood pressure had been elevated by guanidine compounds, a dose of 0.1 gram or even 0.2 gram per kilo was tolerated without a fall in blood pressure. When larger doses, 0.3 to 0.5 gram per kilo, were administered, a reduction of the experimental hypertension occurred, but this dose was lethal and the fall in blood pressure occurred with the death of the animal (Fig. 2). This pharmacological action of choline hydrochloride in hypertension produced by guanidine compounds is in marked contrast to that obtained by the liver extract, which produced a fall to a normal blood pressure without such toxic effects. Dogs, who were the object of experiments with methyl guanidine sulphate and liver extract, appeared perfectly normal 24 hours later.

Modrakowski (16) and Mendel, Underhill and Renshaw (17) have shown that atropine abolishes the effect of choline. In our experiments we have found that atropine injected into dogs whose blood pressure is elevated by guanidine compounds does not inhibit the depressor effects of liver extract. A typical tracing is shown in Fig. 3.

The method of preparing our liver extracts makes it unlikely that choline, which is soluble in alcohol and chloroform, is present in amounts sufficient to exert any depressor effect. The liver extracts have been tested with Rosenheim's periodide and bismuth reagents and do not give a positive reaction for choline.

Do the liver extracts contain histamine? The importance of determining whether the liver extracts contain histamine is quite obvious. Since histamine may be found in the various tissues of the body, it could theoretically explain any depressor effect that extracts of such tissues show.

We have found that 0.05 cc. of a one-per-cent solution of histamine (Kahlbaum) will lower the high blood pressure produced by guanidine. When this dose is repeated or larger doses are given, respiration becomes prolonged, the heart beats become feeble and death may

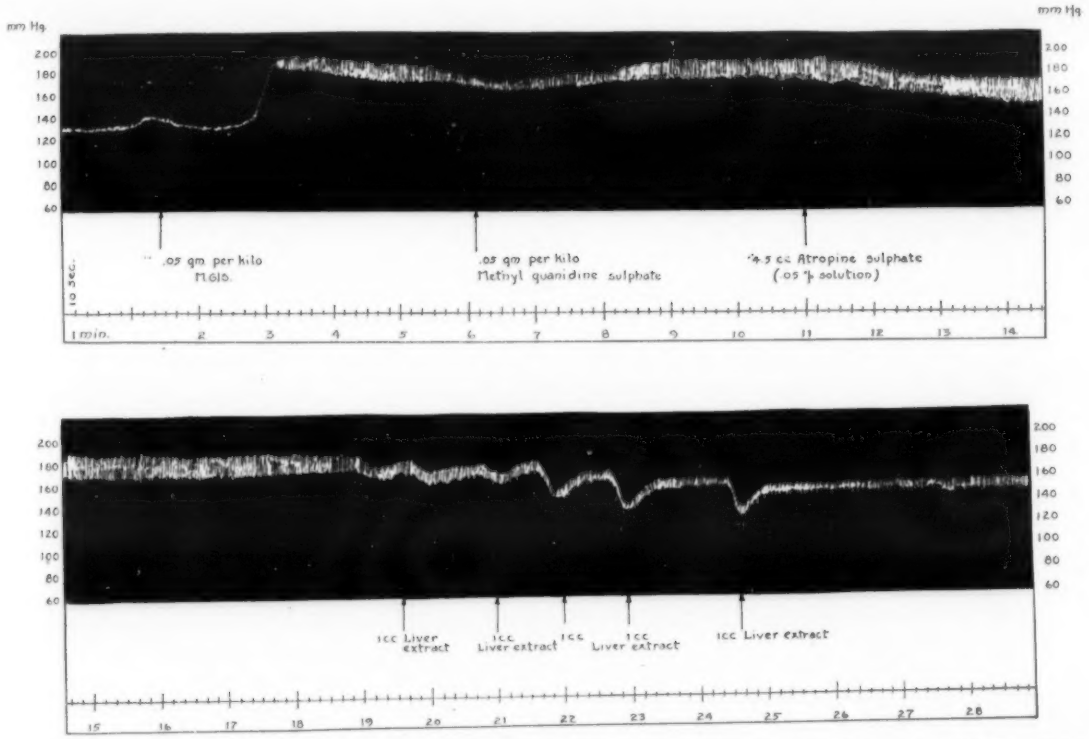

FIG. 3. FAILURE OF ATROPINE TO INHIBIT DEPRESSOR EFFECT OF LIVER EXTRACT UPON HYPERTENSION PRODUCED BY METHYL GUANIDINE SULPHATE

Intravenous injections

result. These toxic effects of histamine are in striking contrast to the lack of toxicity shown by the liver extracts. One sample of liver extract was obtained of such strength that 2 cc. lowered the elevation of blood pressure caused by methyl guanidine sulphate in a dog weighing 10 kilograms (Fig. 4). Another dog weighing 10 kilograms was given single doses of 20 cc. and a total of 68 cc. without effect on its normal pressure and without the appearance of symptoms of toxicity (Fig. 5).

The liver extracts, when tested with virgin guinea-pig uterus, have usually failed to show any contraction, although the uterus was quite active when tested with pituitrin. We have, however, encountered at times preparations of virgin guinea-pig uterus which appeared very sensitive and showed contractions when tested with liver extracts having an acidity of Ph. 2. Such uteri, however, showed equally marked contractions when tested with N/100 sulphuric acid, with N/100 sodium hydroxide, with a mixture of equal parts of N/100 suphuric acid and N/100 sodium hydroxide, with insulin (Lilly) and with Collip's parathyroid extract (Lilly). These results we have interpreted as due to very sensitive uterine tissue and not to histamine, since the presence of the latter could be excluded in the acid and alkaline solutions. Hanke and Koessler (17) have shown that the excised uterus may show contractions with potassium nitrate, potassium chloride, robidium chloride and cesium chloride, and also, as previously stated, to a histamine-free peptone prepared from fibrin (15).

We have tested the liver extracts with p-phenyldiazoniumsulphonate according to the technique of Koessler and Hanke (18), but have failed to obtain a typical color reaction, a yellow color resulting as contrasted with the rose-red obtained with control solutions of histamine.

Hanke and Koessler (10) state that "histamine seems not to be a normal constituent of the herbivorous guinea-pig." We have prepared liver extracts from fresh guinea-pig liver and found them very active in reducing to normal the elevation of blood pressure produced by guanidine compounds.

The liver extracts with which we have worked can be shaken repeatedly with amyl alcohol in alkaline solutions and clarified with

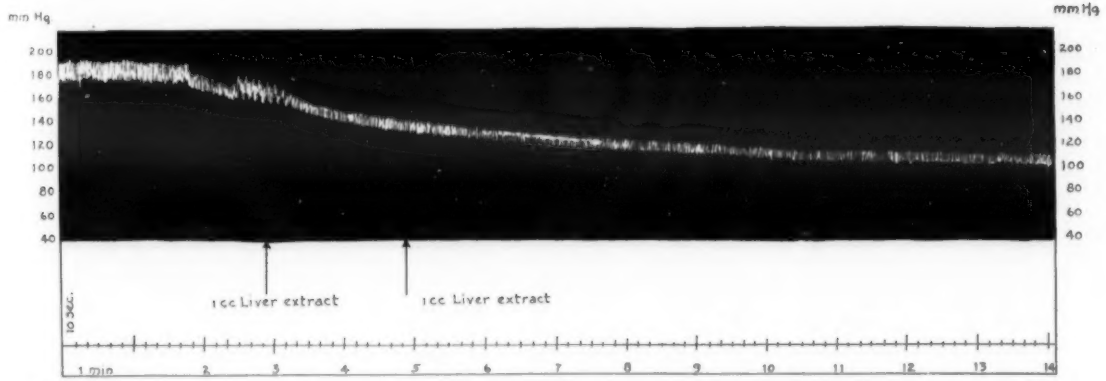

FIG. 4. EFFECT OF LIVER EXTRACT UPON ELEVATION OF BLOOD PRESSURE CAUSED BY METHYL GUANIDINE SULPHATE
Note gradual fall in blood pressure. Intravenous injections of liver extract and of methyl guanidine sulphate

basic lead acetate without losing any of their depressor activity. This is another strong bit of evidence that their activity is not dependent on the presence of histamine, since Hanke and Koessler (10) state that amyl alcohol "removes histamine quantitatively" and that "histamine is adsorbed to a considerable extent by copious precipitates of lead salts."

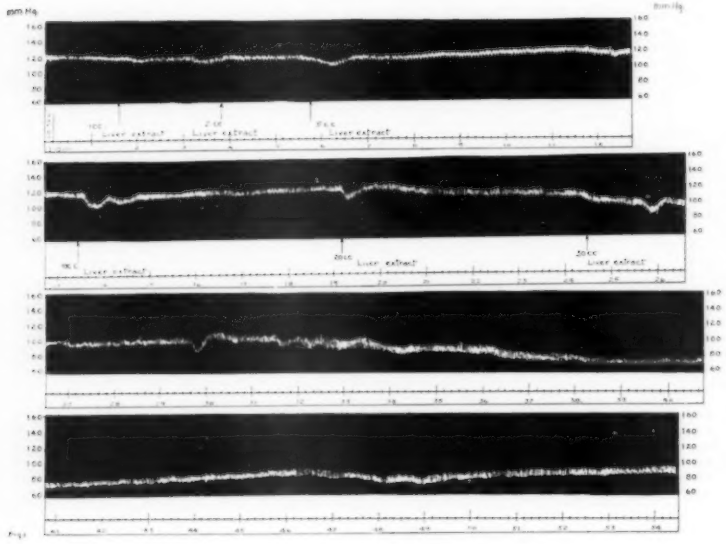

FIG. 5. CURVE SHOWING INTRAVENOUS INJECTIONS OF LIVER EXTRACT TO HAVE NO CONSTANT EFFECT UPON THE NORMAL BLOOD PRESSURE OF A DOG

The coagulation time of the blood was determined five times during the course of the experiment (method of Lee and White). The coagulation time remained at three minutes.

Is the action of the liver extracts a peptone effect? This question is in some ways more difficult to answer than the two preceding because of the difficulty in defining chemically just what we mean by a peptone.

In the method of preparing liver extracts by alcoholic fractionation the peptones remain in solution in the discarded filtrate, and the final preparation shows no precipitate when treated with phosphotungstic

acid or with absolute alcohol. Liver extracts prepared by some of the other methods contained peptones but, after these had been removed with absolute alcohol, the liver extract still had a marked depressor effect.

The marked shock that follows the intravenous injections of peptones in animals has been entirely absent in our experiments. The great delay in the coagulation time of the blood, which is a striking feature of peptone shock, has not been encountered in our experiments. The most characteristic feature of the blood pressure changes following the injection of peptone is a very rapid, almost sudden fall. While we have at times encountered such rapid falls in the high blood pressure due to guanidine after the injection of liver extract, the curve usually obtained shows a more gradual descent (Fig. 4). As further evidence against the supposition that the activity of the liver extract depends upon peptone may again be mentioned the fact that a control animal may withstand thirty-five times the dose that lowered a hypertension due to methyl guanidine sulphate without showing any fall in blood pressure.

The liver extracts, as previously stated, produce a marked lowering of both systolic and diastolic blood pressure in patients suffering from arterial hypertension. We have observed a fall in systolic blood pressure as great as 50 mm. within one hour following subcutaneous or intravenous injections of 2 to 5 cc. of liver extract. Such a fall has been accompanied by no unpleasant symptoms such as one might expect were the result due to histamine or peptone. The extract, when injected intradermally produces only a slight transitory burning sensation without the appearance of urticaria or allergic phenomena.

SUMMARY

Further investigations of an extract prepared from the liver, show that it has a marked effect in lowering the hypertension produced by guanidine compounds.

The activity of this extract apparently is not due to choline, histamine or peptone.

We have not obtained any conclusive evidence that this extract contains choline or histamine.

It is a pleasure to acknowledge the assistance of the Lilly Research Laboratories in preparing and supplying liver extracts and to thank Miss Vera Johnsmeyer for valuable technical assistance.

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THE EXPERIMENTAL PRODUCTION OF ANNULAR LIGAMENTS, AS AN EXAMPLE OF THE INFLUENCE OF FUNCTION UPON THE DIFFERENTIATION OF CONNECTIVE TISSUE[1]

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HISTORICAL

Stress and strain were first considered as definite factors in the development of connective-tissue structures by Wilhelm His. In his *Häute und Höhlen des Körpers* (1) he describes the effect of these factors as follows:

> The progresss of the developmental relations of connective tissue may be stated as follows. At every place where connective tissue is exposed to a constant or often repeated pulling action, there is formed a fibrous band, *e.g.*, a tendon, the direction of whose fibres is parallel to the direction of pull; where a connective-tissue layer experiences a supporting or oft-repeated pressure in the same direction, there is formed a fibrous disc, of greater or lesser thickness, of laminated structure, with generally a cross-fibre formation, the fibres of which run in planes perpendicular to the direction of pressure. Finally, where the connective tissue experiences mild grades of tearing action there arise loose layers of connective tissue, with cross direction of fibres, and with much enclosed mucus or fat. According to this conception, a muscle develops its tendon as well as its fascia, the growing cartilage begets its perichondrium, the eye its capsule, and the blood vessel its sheath. . . . . It is now possible, at least to a certain degree, to trace back the growth relations of the connective-tissue organ to the particular kind of mechanical action. For example, if a tissue mass formed of scattered cells and a ground substance is stretched equally in all directions, then apart from the growth possibilities inherent in them, the cells have no reason to grow out in one direction more than another. If now there takes place a continuous pull on the tissue, then the latter will assume less thickness in the direction of the pull than in the plane

[1] Submitted for publication July 6, 1925.

perpendicular to it, and thereby the conditions are disturbed for the uniform spreading out of the growing cells (as also for the frequently present wandering cells), the cells will grow out easiest in the direction of least resistance, *i.e.* in the longitudinal direction.

The above conclusions are based on anatomic considerations to which His added his explanaton of the sequence of events. In general, these conclusions have received confirmation at the hands of later workers, many of whom have lost sight of the fundamental facts at the basis of their results.

Shortly after this analytic work of His, a series of brilliant researches succeeded in establishing the influence of stress and strain on bone form and bone architecture. Hermann von Meyer first called attention to the relation between the internal structure of bone and the mechanical forces to which this bone was subjected. Julius Wolff on the basis of researches formulated these ideas into a law (4). Experimental work, continuing to the present time, together with careful analyses and reanalyses of the architecture involved, has very thoroughly established the principle, although some of the details are still in controversy.

In contrast with this work on bone we find that the problem of the influence of function on the development of connective tissue is in practically the same state that it was in 1865. Probably the reason for this condition of affairs is to be found in the nature of the tissues themselves. Bone lends itself more readily to testing and analysis if for no other reason that that its margins are definitely outlined, and its form is retained without the use of fixing agents. His republished his paper in 1903 stating that nothing in the intervening time had caused him to change his ideas. It might be added that no work had appeared to cause him to amplify his thesis.

Wilhelm Roux, the great mechanist of the past century, believed at one time that function and action were the sole factors in developing connective-tissue structures. Later, however, he came to the conclusion that this idea, which was similar to that of His, was insufficient to explain the very intricate anatomy of certain connective-tissue structures (3), and he felt himself forced to classify some of these structures as non-functional and hereditary in character. He felt that the life of every animal was divided into two stages, a

first period of embryonic life in which the form was determined by "directly inherited" characters, and a second stage, one of further differentiation and of independent growth. In his own words "There must be distinguished in the life of all the parts (*i.e.*, organs), two periods, an embryonic in the broad sense, during which the parts develop, differentiate, and grow of themselves, and a period of more complete development, during which growth, and in many cases also the balance of assimilation over dissimilation, can come about only under the influence of stimuli" (2, p. 180).

The more or less unsettled state of the ideas in this field was brought out by Fick in 1904 who said (7, p. 44):

> Indeed it seems to me to be insufficient to assign only the pull or tension in active and passive movements as the causal impetus for the development of bands, since, for example, the collateral ligaments of the hinge-joints will certainly not have to bear any strong pull during normal movement, because no muscles are applied to the joint in exactly their direction. On the other hand, one plainly sees how the ligaments of the lower extremity, which have to withstand the stronger pulls, are considerably heavier than those of the upper (extremity). From these suggestions it follows that, even in syndesmology, it still remains for causal research to solve certain essentials.

In 1904, Oscar Levy (8), a pupil of Roux and of Eisler, brought forward some very interesting and instructive data in favor of the importance of function in determining form of connective-tissue structures. He used the Achilles tendon of the rabbit for his experiments. He showed that when this tendon is divided, and mechanical action between or on the cut ends is hindered or removed entirely, by placing the limb in a cast, by excising the muscle supplying the severed tendon, or by cutting the nerve to that muscle, there was no regeneration of the tendon; whereas in the cases in which no such devices were used to hinder motion, the tendon promptly regenerated. Even more important and instructive was another of his experiments: after dividing the Achilles tendon, he placed two silk sutures in the soft tissues at the level of the cut. He then incased the leg in a plaster dressing to prevent pull in the longitudinal direction, allowing the silk sutures to come out through the sides of the cast. He then exerted a continuous pull on these silk threads at right angles to the long axis of the leg, maintaining this pull for a period of three to

four weeks. At the end of 23 days, and at the end of 26 days, respectively, he sacrificed his animals, and found that the microscopic sections through the operated areas showed that the connective tissue between the two silk sutures was arranged with the long axis of the cells in the direction of the pull between the threads, *i.e.*, perpendicular to the long axis of the limb and of the original tendon, the direction they would normally have taken if the lateral pulls had not been exerted.

Jiro Kaneko (9) another of Roux' pupils, in the same year (1904) showed the importance which pulls on connective tissue have in developing definite structures. He attempted to reproduce tendinous arcs and arcuate fibres, and succeeded in reproducing microscopic ones by a variety of methods. For example, he passed a silk suture through a flat muscle such as the latissimus dorsi, and then hitched the ends of the thread to the animal's skin. The movements of the skin when the animal (rabbit) hopped around imparted an intermittent tugging action to the suture. Kaneko noted that there was first more or less necrosis where the suture pulled on the muscle, followed by the development of a type of undifferentiated connective tissue, whose cells later assumed the direction one sees in a tendinous arc. He also was able to cause the development of arcuate fibres around the edges of holes cut in flat muscles, and found evidence of the development of arc-like fibres around a suture with which he had encircled a bone beneath a muscle insertion, thus simulating the arcuate fibres around perforating circumflex arteries.

In recent years one finds no contributions to this study except in the realm of tendon regeneration. This subject is one of much practical as well as of theoretical importance, and has interested a great number of investigators. The work of Marchand (6), Rehn (10), Sever (12, 14), Lange (11), and of many others on tendon regeneration shows that these structures regenerate very completely and satisfactorily, if given suitable conditions. Lange and Sever (*loc. cit.*) have shown the advantage of an artificial connecting link between the severed ends. They do not specifically refer to the necessity of movement in the tendon, a factor which we believe is essential for the development or redevelopment of a connective-tissue structure serving the function of a tendon. Levy pointed this out clearly.

Henze and Mayer (16) call attention to it again, in connection with the speed of regeneration, but do not clearly state that it is an essential factor. The work of Lewis and Davis (13) on direct transplantation of tendon and fascia throws some interesting light on this subject. They say: "Transplanted tendons which assume function early do much better than those which are immobilized for long periods of time, both regarding the viability of the transplanted segment and the freedom of movement." They also showed that tendon segments one inch to one and a quarter inches long, transplanted into subcutaneous fat, tend to become progressively smaller, although they retain their microscopic structure. Similar tendon segments transplanted between the ends of divided tendons, enlarge, or retain their original size, although their structure changes slightly, so that they can be distinguished microscopically, even after considerable periods of time, from normal tendon. They do not, however, point out that the atrophy of subcutaneously placed tendon segments and the relative hypertrophy of functionally active transplants are due to the functional activity.

Eisler himself (15), in his *Muskeln des Stammes*, seeks throughout to explain the structure of connective tissues on a functional basis. For example, he analyses the forces acting on the lacertus fibrosus of the biceps brachii, and shows that it has a very definite pull placed upon it when the forearm is in supination, this presumably being the reason for its presence.

EXPERIMENTAL

In an endeavor to obtain definite experimental evidence as to the influence of function in the development of connective-tissue bands and sheets, we sought a structure which would possess sufficient definiteness and consistence to make results decisive. Annular ligaments seemed to afford a structure that possessed considerable strength and density, and at the same time had rather definite borders. Annular bands occur only at those joints where long tendons cross the joint and produce angulation. These bands lie at the apex of the angle, with their fibres in the direction of the pull exerted by the tendon in its effort to leave the joint during action. The direction of pull (and the paralleling direction of the connective-

tissue fibres) is at right angles to the muscles and tendons of the regions (*cf.* Fig. 1). This makes differentiation easy.

In the hind leg of the dog the annular ligament at the ankle lends itself particularly well to experiment, for it is possible to remove part of the band without interfering with the use of the limb and without altering the forces normally at work in the part. A cross section through the dog's ankle (Fig. 2) shows that all the tendons pass through a lateral compartment. We sought to experiment on the medial compartment. The septum in the osteo-fibrous canal

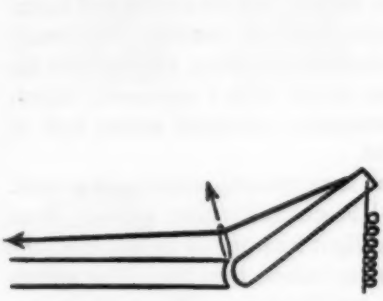

FIG. 1

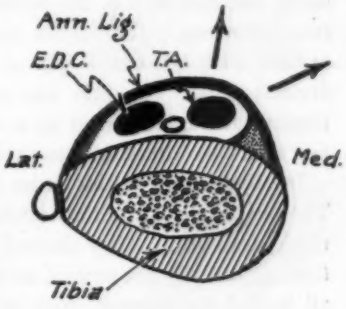

FIG. 2

FIG. 1. DIAGRAM TO SHOW THE MECHANISM BY WHICH PULL IS EXERTED ON THE ANNULAR LIGAMENT BY TENDON IN ACTION

FIG. 2. DIAGRAMMATIC CROSS-SECTION OF THE DOG'S ANKLE AT THE LEVEL OF THE ANNULAR LIGAMENT

Ann. Lig. = annular ligament. T.A. = tendon of tibialis anterior muscle. E.D.C. = tendon of extensor digitorum communis. Lat. = lateral. Med. = medial.

has been said to be the tendon of the rudimentary peroneus tertius muscle (19).

Experiments

We planned first of all to remove this medial portion of the annular band to see if it would develop again, and if so, the time required and the completeness of the new structure. Accordingly, the following series was begun.

Series 1. Removal of the medial portion of the annular ligament (Dogs 1, 2, 3, 7).

Operation. The skin over the left ankle was shaved, washed with soap and water and then with alcohol. The animal was anaesthetized with ether. The skin was then painted with tincture of iodine. A mid-line incision was made over the front of the ankle, through the skin and subcutaneous tissues. The annular ligament was identified, and isolated by sharp dissection. Bleeding points were clamped and tied with fine silk. The ligament was freed at its upper and lower margins, and a grooved director passed beneath the medial portion. The ligament was freed medially to its periosteal attachment, and laterally to the septum dividing it into medial and lateral compartments. The medial portion was then carefully and cleanly excised with scissors, a gap of about 1 cm. being left between the divided ends. The skin was then closed with a continuous subcuticular suture, reinforced by a continuous epidermal suture, both of fine silk. No dressing was applied.

In all the dogs in this series the same general technique was used. The dogs began walking around immediately after recovery from the anaesthetic. They showed a slight limp for 24 to 48 hours, and then apparently got around as well as before operation. The wounds all healed *per primam*, with not the slightest evidence of infection. Dog 3 died of pneumonia three days after operation. The others were sacrificed as follows:

Dog 1[2] after 11 weeks.

Dog 2 after 7 weeks.

Dog 3 after 5 weeks.

Results in Series 1. Dog. 1. At the end of 11 weeks there had regenerated on the operated side a new annular ligament (medial half), which grossly was so nearly like its mate on the opposite side in size, shape and general structure, that it was difficult to say which was the operated, and which the unoperated side (*cf.* Fig. 3).

Dog 2. At the end of 7 weeks there had regenerated in this animal, on the operated side, a medial portion of annular ligament, similar in shape and general structure to the one on the other side, but not nearly so heavy or thick (Fig. 4). Microscopic sections through this new tissue showed a histologic structure very similar to that through the ligament on the other side.

[2] Operated upon by Dr. Beverly Douglas.

FIG. 3

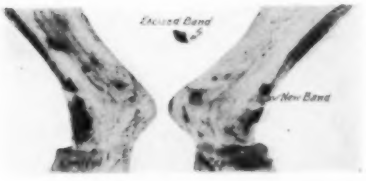

FIG. 5

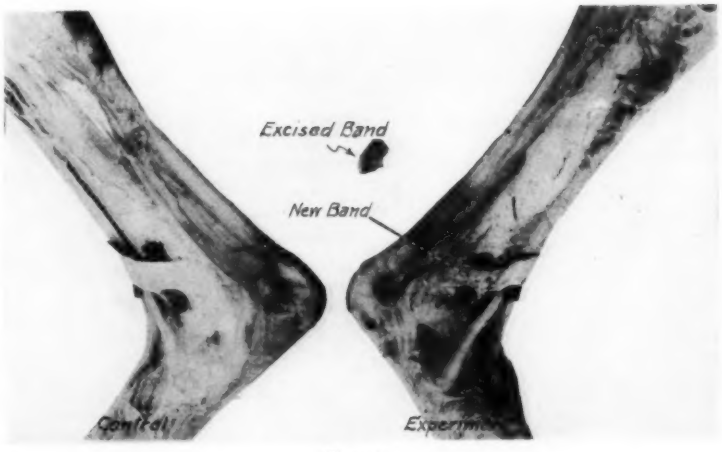

FIG. 4

FIG. 3. DOG. 1. SERIES 1. TO SHOW NEW ANNULAR LIGAMENT DEVELOPED IN 11 WEEKS

FIG. 4. DOG 2. SERIES 1. EXCISION OF MEDIAL PORTION OF BAND. NEW BAND DEVELOPED IN 7 WEEKS

FIG. 5. DOG. 7. SERIES 1. EXCISION OF MEDIAL HALF OF BAND. NEW BAND DEVELOPED IN 5 WEEKS

Dog 7. At the end of five weeks in this animal there had regenerated on the operated side, the medial portion of the annular ligament as a relatively much broader but also thinner band than on the other side, *i.e.* it was a less definite structure than in Dogs 1 and 2, fading almost imperceptibly into the surrounding connective tissue, and appeared therefore as a broad, thin layer, of more or less undifferentiated connective tissue, which had its greatest thickness in the position where the excised portion had lain originally (Fig. 5).

When the dissection of Dog 1 showed that the annular ligament would develop under the influence of function, it was necessary to show whether it would develop in the absence of functional influences. Accordingly a second series of experiments was started. In this series the medial part of the annular ligament was removed, and in addition all the muscles having tendons passing beneath the annular ligament were excised, thereby eliminating any pull upon the tissue in the region of the excised band. Vessels and nerves were preserved, the muscles alone being severed.

Series 2. Removal of the medial half of the annular ligament. Division of the tendons which pass beneath the ligament, just proximal to the latter, combined with excision of the muscles of these tendons. Application of a plaster cast (Dogs 4 and 5).

Operation. Skin prepared by the usual technique. Ether anaesthesia.

A mid-line incision was made over the front of the left ankle, through the skin and subcutaneous tissues. The annular ligament was identified, and isolated as in the previous operations. The medial portion of it was excised as in the operations of Series 1.

The skin incision was then continued up the front of the leg to the knee. The deep fascia was divided in the line of the skin incision. The muscles on the front of the leg were divided just below their origin, the division extending down to the bone and the intermuscular septum, preserving the large artery, vein and nerve lying posterior to the muscles. The muscles were then freed down to their tendons, the muscular branches of the vessels being divided between clamps as encountered. The tendons were freed down to the level of the upper edge of the annular ligament, where they were cut across, allowing the complete removal of the muscles and tendons from their

origin down to this point. Silk was used throughout for ligature and suture material. The deep fascia was closed with a continuous suture to help to obliterate dead space. The skin was closed with a continuous subcuticular suture, reinforced with a continuous epidermal suture. Dry dressings were applied, the leg was padded with cotton, and incased in a plaster of Paris dressing from the paw to the knee, to prevent as far as possible any motion at the ankle joint.

Two dogs were operated upon in this series, essentially the same operative technique being used in each case. The animals limped around on the splinted leg in about 48 hours, and apparently suffered little inconvenience from the cast. They were sacrificed as follows.

Dog 4 after 7 weeks.

Dog 5 after 5 weeks.

Results in Series 2. The results were identical in both animals. At the end of 7 weeks and at the end of 5 weeks, respectively, careful dissection failed to reveal the slightest suggestion of the development of any connective-tissue structure which resembled or occupied the position of the excised portion of the annular ligament. The cut ends could be easily identified, and they looked almost exactly as they had immediately after the excision (Figs. 6, 7).

It was next desired to determine whether a band could be produced in an area where one had not previously existed. For this purpose a series of tendon transplants was devised: in one type the tendon was divided and resutured upon the surface of the band; in another type the band was divided and resutured beneath one of the tendons. Both of these methods allowed the tendon to pull on the connective-tissue superficial to the annular ligament.

Series 3a. Division of the tendon of the tibialis anticus. Transplantation of the tendon to a position superficial to the band, and resuture of the tendon (Dogs 6 and 8).

Series 3b. Division of the annular ligament in its lateral portion, with resuture of the band beneath the tendon of the tibialis anterior (Dogs 9 and 10).

Series 3a. Operation. Skin preparation—hair removed with sodium sulphide solution. Skin washed with water and then with alcohol. Tincture of iodine then applied. A slightly curved skin incision was then made, beginning in the midline just above the ankle,

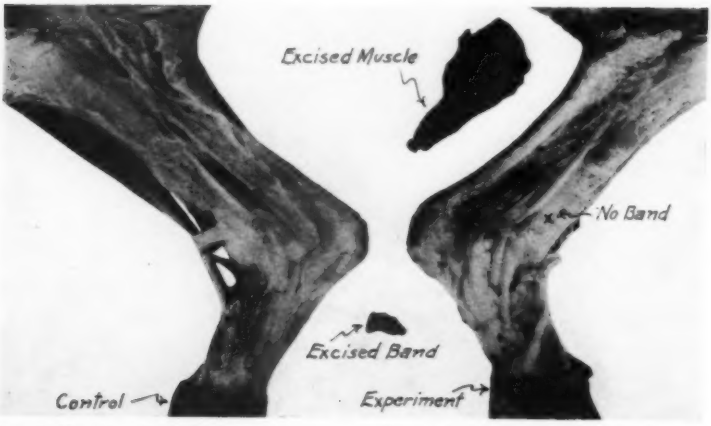

FIG. 6. DOG 4. SERIES 2. EXCISION OF BAND. EXCISION OF MUSCLES. APPLICATION OF CAST. SHOWS FAILURE OF NEW BAND TO DEVELOP IN 7 WEEKS

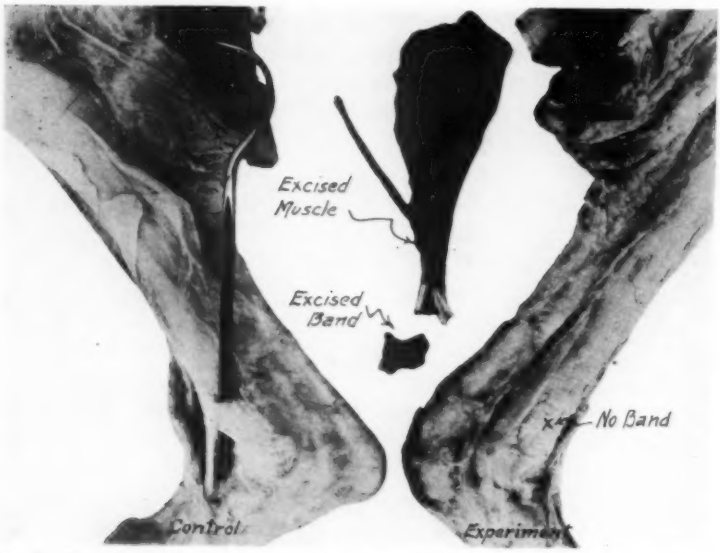

FIG. 7. DOG 5. SERIES 2. EXCISION OF BAND, AND OF MUSCLES. CAST. FAILURE OF NEW BAND TO DEVELOP IN 5 WEEKS

and extending downwards and medially along the course of the tibialis anticus tendon. The tendon was isolated just where it begins to curve around the medial side of the leg. It was divided at this point. Mattress sutures of fine silk were placed in both cut ends. The tendon sheath was then split, and the tendon lifted out by dividing the mesotendon. The tendon was freed in this manner up to the annular ligament, and isolated just above the ligament. It was then pulled from under the ligament, placed superficially to it, and the tendon ends approximated by tying the mattress sutures previously placed. The line of suture was reinforced by a few interrupted sutures of fine silk. The deep fascia and tendon sheath were then closed over the replaced tendon with several interrupted sutures, to hold the tendon in place. The skin was closed with a continuous subcuticular suture, reinforced with a continuous epidermal suture. A dry dressing was applied, and the leg placed in a plaster dressing from the foot to the knee.

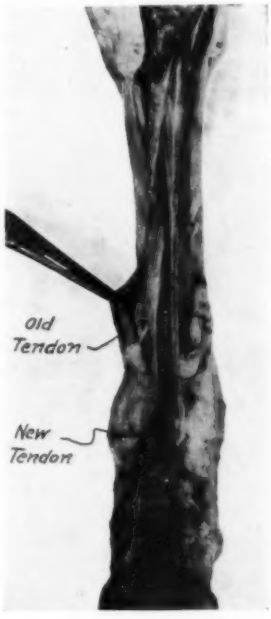

FIG. 8. DOG 6. SERIES 3a. DIVISION OF TENDON WITH RESUTURE ABOVE BAND. SHOWS NEW TENDON AND WIDE, NEW BAND. VIEW FROM FRONT

Two dogs were operated upon in this series. Dog 6 was allowed to remain in a cast for four weeks. The cast was then removed, and the animal ran around in the runway with the other dogs for six and a half weeks with no support on the leg. Dog 8 died of pneumonia 4 days after operation.

At autopsy on Dog 6, it was found that the sutures in the tendon had failed to hold, and the tendon ends had separated widely. A rather complex picture was shown in the operation area. A new tendon, or a structure resembling a new tendon, had developed, filling in the gap between the separated tendon ends. This new tendinous structure was beneath the old

annular ligament. It was 5 cm. long. The large proximal stump of the tendon was found to be at the upper margin of the old annular ligament. This annular ligament was augmented by a thinner annular band, continuous with the original one, and much wider, fully three times its width. No bands of any nature are normally found in the area to which this structure had extended (Figs. 8 and 9).

Series 3b. Operation. Skin preparation as in the preceding experiment. A mid-line incision was made over the front of the

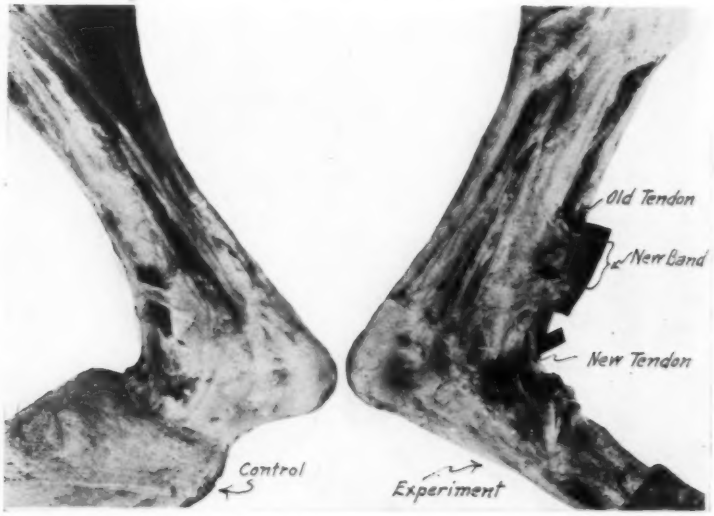

FIG. 9. DOG 6. SIDE VIEW

ankle, through the skin and subcutaneous tissues. The annular ligament was identified, and isolated by sharp dissection. It was divided in the mid-line, *i.e.* in the lateral compartment. The tendon of the tibialis anterior muscle was lifted to a position superficial to the ligament, and the latter was sutured deep to it with mattress sutures of fine silk. The skin was closed with the usual subcuticular and epidermal sutures. No dressings were applied.

Two dogs were used in this series. In both cases there was no evidence of infection, and the wounds healed *per primam*. The

animals were apparently not inconvenienced by the operative procedure. The dogs were sacrificed at 5 weeks and at 3 weeks, respectively.

Results in series 3b. Dog 9 was killed 5 weeks after operation. Dissection in the operative field showed that the sutures in the annular ligament had failed to hold. As a result the ends were far apart, but the gap was well bridged by a definite band of connective

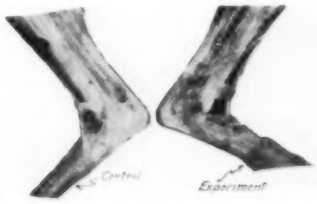

FIG. 10

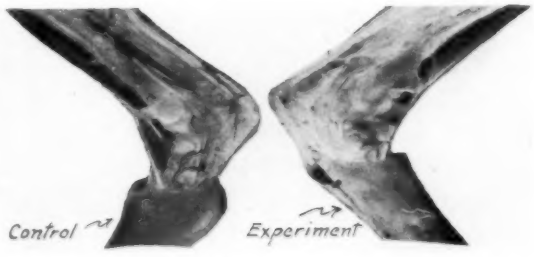

FIG. 11

FIG. 10. DOG 9. SERIES 3b. DIVISION OF ANNULAR BAND WITH RESUTURE BENEATH TENDON. NEW BAND IN 5 WEEKS

FIG. 11. DOG 10. SERIES 3b. DIVISION OF ANNULAR BAND WITH RESUTURE BENEATH TENDON. NEW BAND IN 3 WEEKS

tissue, which extended over the entire front of the ankle, passing over the tendons of both muscles, and serving the function of an annular ligament (Fig. 10).

Dog 10 was killed at the end of 3 weeks after operation. There were findings similar to those in Dog 9, but the bridging band of connective tissue was less fibrous in nature. Upon pulling on the tendons passing beneath this structure, its function as a restraining band for the tendons was readily evident (Fig. 11).

An attempt was made to duplicate these experiments on four rabbits. In all of them the skin was prepared by removing the hair with sodium sulphide solution, and then washing with water and alcohol. Tincture of iodine was then applied. Ether anaesthesia was used in all cases.

Rabbits 1 and 2. In these two animals the entire annular ligament of the left leg was removed. In the rabbit there is no division of the ligament into two compartments as in the dog. The ligament is relatively much thicker and narrower than in the dog, with very definite outlines. In cross-section it is almost rectangular, instead of flattened and oval. For our purposes it was thought best to remove the entire ligament. In accordance with this idea, the left band in both of these animals was removed from its periosteal attachment on one side to its periosteal attachment on the other. The procedure was carried out through a mid-line incision over the front of the ankle. The dissection was done with a knife and scissors. The skin was closed with a continuous suture of silk.

Rabbit 2 developed a wound infection, and died about 3 weeks after operation while both authors were absent from the city on vacation. No autopsy was performed.

Rabbit 1 was sacrificed 7 weeks after operation. The wound had healed perfectly. Dissection revealed the presence of a new annular ligament, similar in its general appearance and shape to the original band removed, but not quite so distinct in its outlines, *i.e.* it was not so thick as the original structure, but was somewhat wider, and faded out more gradually into the surrounding tissues (Fig. 12).

Rabbit 3. In this animal the annular ligament was divided, and resutured beneath (deep to) the tendon of the extensor communis digitorum. The skin was closed with silk. No dressing was applied.

This animal was sacrificed 5 weeks after operation. As in the corresponding experiment on the dog, the suture in the annular ligament had failed to hold, and the ends had separated, allowing the tendon to resume its original position in relation to the band. A new band, or a structure serving the function of a band, had developed at the site of the original one. It was not quite so heavy, nor so well formed as the one on the control leg, but was a very serviceable annular ligament (Fig. 13).

Rabbit 4. The operation consisted in removing the annular ligament as in Rabbit 1, combined with division of the tendons which passed beneath it at the level of its proximal edge, and with excision of the muscles of those tendons. The skin was closed tightly, a dry dressing was applied, and the leg was put in a plaster cast. At the end of 6 weeks the cast was removed, and the animal was killed. Examination of the operative field showed that there was no band of connective tissue over the front of the ankle in the position previously occupied by the annular ligament. After skinning the leg, there was no subcutaneous tissue left over the front of the ankle, and one saw exposed the cut ends of the tendons, the cut ends of the annular

FIG. 12 FIG. 13 FIG. 14

FIG. 12. RABBIT 1. EXCISION OF BAND. NEW BAND IN 7 WEEKS
FIG. 13. RABBIT 3. DIVISION OF BAND, WITH RESUTURE BENEATH TENDON. NEW BAND IN 5 WEEKS
FIG. 14. RABBIT 4. EXCISION OF BAND AND MUSCLES. CAST. NO BAND IN 6 WEEKS

ligament, and the bone. There was no regeneration of connective tissue at the site of the annular ligament (Fig. 14).

Summary of experiments

To determine whether the influence of function as a factor in the differentiation of connective-tissue bands could be demonstrated by experiment, we used the annular ligament at the ankle in the dog and rabbit. A portion of this band uniformly grew again after excision, when the part was allowed to remain functionally active. When the musculature exerting the pull in the region was also removed, the band failed to redevelop. By altering the application and the direction of the physiologic pull, the form and the position of the fibrous

bands were correspondingly changed. In each case, the connective-tissue fibres formed in the same direction as the pull was exerted.

DISCUSSION AND CONCLUSIONS

We feel that this series of experiments is to be interpreted as showing that the various connective-tissue bands of the body are present as *the result of development in response to mechanical factors*. This conclusion presupposes the ability to form fibres under strain physiologically applied as a fundamental property of connective tissue. We shall not discuss this phase, which has been studied by Isaacs (18) and others.

Although we are not prepared to submit evidence at the present time, we feel that the continuance of these functional factors is necessary in maintaining the integrity of these structures. This opinion is in agreement with the experiments of Brooks (20), who found that tendon and fascia long immobilized decreased in elasticity and strength. As for elastic tissue, although some researches attempted by us have not been conclusive, we believe that this tissue develops where sudden, strong strain is applied followed by quick relaxation.

Our experiments do not throw any light on the first appearance of fibrous connective tissue in the embryo. Many ligamentous structures are said to be rudimentary muscles and the like. We feel that, although some of these structures are vestigial remnants, their persistence into adult life is due to the pull exerted on them. For example, while we believe that the peroneus tertius tendon in the dog may be incorporated in the septum beneath the annular ligament, we are certain that this septum is really a reflex sling developed in response to the tendency of the tendon of the tibialis anterior to veer medialwards during action (Fig. 2). There are many bands in the body which are described as inherited structures. We think that all of these have been under pull during development, and that they are under pull in their adult state. As a case in point, one of us (Batson, 21) has shown that ligaments such as the coracoacromial ligament, although joining two points on the same bone, are actually under considerable pull at times, owing to the elasticity of the bone. The dura mater cerebri and spinalis apparently present

a similar problem, the falx cerebri probably being ligamentous in character because of the forces exerted upon it by changes in the shape of the skull. The thickening of the dura beneath a bone defect such as a decompression wound is no doubt a response of this structure to increased strain.

The various layers of subcutaneous fibrous bands (deep fascias) can be explained in a similar fashion. This method of study of these structures shows why the fibrous subcutaneous fascias are so much heavier and the layers more numerous in individuals with a heavy panniculus adiposis. This property of connective tissue to form fibres renders the formation of the "ligaments of Cooper" in the breast obvious.

In our study of the periosteum in relation to annular bands it seemed to us that the periosteum for each bone presented a definite arrangement of fibres, and that the arrangement always corresponded to the tension applied to it in the bending of the bone.

If the foregoing be accepted, we must discard the hereditary explanation for the presence of bands in the body, and must not consider them as being there in order to protect the body structure against unusual displacements, but when they are found, we must search in the living body for the factors normally and constantly present which produce them.

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STUDIES ON THE EXPERIMENTAL PRODUCTION OF PREMATURE SEPARATION OF THE PLACENTA

A Preliminary Communication

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In summing up the present state of our knowledge concerning the etiology of the premature separation of the normally implanted placenta, Williams[1] recently stated: "As yet we are entirely ignorant of the ultimate cause of the accident." At the same time he intimated that its sudden onset, its frequent occurrence in toxaemic or eclamptic women, the occasional demonstration of degenerative lesions in the kidney or liver, and the presence of albuminuria in a large proportion of the cases led him to believe that a toxaemia of some kind was responsible for the production of at least the majority of the serious cases. Besides the external bleeding or concealed hemorrhage, shock, severe pain in the abdomen, and a ligneous consistency of the uterus are regarded as the prominent clinical symptoms of this serious complication, but in many instances the shock is out of proportion to the amount of blood lost.

Couvelaire and Williams were the first to direct attention to the fact that, in severe cases at least, the condition is accompanied by characteristic lesions. The uterus assumes a peculiar, coppery, metallic appearance and sometimes presents fissures on its peritoneal surface, while the broad ligament and occasionally the tubes and ovaries are engorged with blood. Upon histological examination the uterine lesion consists in intramuscular hemorrhage, which leads to disassociation of the muscle fibres and which is due to damage to the walls of veins of small and moderate calibre, while outside of the hemorrhagic areas the connective tissue is spread apart by oedema.

The decidua basalis presents no signs of inflammation, but hemorrhage into its depths appears to be the immediate factor in bringing about the separation of the placenta.

[1] *J. Obst. & Gyn. of the British Empire*, 1925, xxxii, No. 2.

When one takes into consideration the hemorrhagic lesions associated with the condition, and furthermore recalls the fact that the shock is frequently out of proportion to the amount of blood lost and that the blood pressure is markedly lowered, one inevitably calls to mind the well-known picture of experimental histamin-intoxication. The question, therefore, suggested itself, whether premature separation of the placenta and its accompanying phenomena could not be reproduced by the administration of chemically pure histamin to pregnant animals. Accordingly, it seemed advisable to carry out some experiments in rodents and carnivora, bearing in mind the great disparity in the placentation in various classes of animals, as well as the difference in their sensitiveness toward histamin.

The discoidal placenta of the guinea-pig exhibits a reasonable similarity to that of human beings, particularly in that the whole entity of the villi is attached to the periphery—ectodermal giant cells and ectoplacental entoderm—by plasmodial roots suggestive of the fastening villi in the human placenta. Since the syncytial columns give rise to a meshwork containing maternal blood, they present a functional similarity to the intervillous spaces in the human placenta. At the same time, it should be remembered that the area of attachment of the guinea-pig's placenta becomes progressively smaller with the advance of pregnancy, so that at term the organ is attached to the uterine wall by a peduncle, like a button to a coat. For this reason one should not expect retroplacental hemorrhage and placental separation to occur as in woman.

Cats were chosen for our experiments on account of their peculiar sensitivity to histamin, but in view of the labyrinthine structure of their placenta and its loose attachment to the uterine mucosa, one could scarcely expect to produce premature separation by the same mechanism as in human beings.

Our experiments were conducted upon ten guinea-pigs and four cats, and, with the exception of chloralose in one instance, no anaesthesia was employed. Histamin was given intravenously or intracardially in the dilution of 1:1000 down to 1:3000 per kilo of body-weight. By way of control, two other animals were injected with histamin-free peptone.

Immediately a striking gross result was obtained, the uterus going into tetanic contraction, its vessels, as well as those of the broad ligament, becoming immensely engorged, while the animal passed into a condition of shock with a marked fall in blood pressure.

Upon histological examination, the invariable result in guinea-pigs was that in different places the fastening plasmodial roots had become detached to a greater or lesser extent and hemorrhage had separated in part the placenta from its basal tissue. In the cat the placenta did not show signs of separation, but in this connection it must be borne in mind that its structure differs entirely from that encountered in the human placenta. Moreover, a noteworthy phenomenon was observed in the uterine mucosa in this series of experiments, namely, a conspicuous hemorrhage extending along the course of the blood-vessels, while the uterine glands adjacent to the placenta were filled with fresh blood, which in places lifted up the epithelial covering of the uterine mucosa. Within the uterine wall the occurrence of a marked oedema, spreading apart the muscle bundles, was a striking feature. In the guinea-pig, as well as in the cat, the occurrence of thrombi in the veins of the decidua and of other organs, especially the liver, could be demonstrated. In some of our experiments the abdominal cavity contained a variable amount of free fluid, which was highly conspicuous in a few instances.

The changes encountered in the livers of the cats aroused our special interest, peripheral necrosis and stagnation of the bile being the most prominent features. A precipitation of bile pigment within the liver cells and the presence of bile thrombi indicated that this stasis had occurred particularly in the inner half of the lobuli. Thrombi were noted in the blood-vessels of the decidua and liver, in some instances as hyalin thrombi, in others as clustered erythrocytes with platelets. Since marked degenerative changes occurred in the epithelium of the convoluted tubules of the kidney, the above observations bear a striking similarity to the characteristic lesions occurring in both organs in eclamptic patients.

The results obtained are in harmony with the recent tendency pointing to the association of premature separation of the placenta with a toxaemic process, and indicate that a sudden access of hista-

min to the circulation of the pregnant woman might well account for the sudden appearance of the accident in question with its train of alarming symptoms.

In a more extended paper with illustrations the organic lesions will be described in detail, and reasons will be adduced which may afford a theoretical possibility for the sudden appearance of histamin in the pregnant woman.

BACILLUS BRONCHISEPTICUS INFECTION IN A CHILD WITH SYMPTOMS OF PERTUSSIS

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On April 12 (Easter) a young rabbit was given to a child, five years of age, in the family of the author. The little girl fondled and caressed her pet a great deal. The rabbit had a slight diarrhoea and after a few days had a mild "snuffles." There was scarcely any nasal discharge, but the rabbit sneezed frequently and the child was not allowed to handle it as much as formerly. About ten or twelve days after Easter the little girl began to cough at night. There were usually two or three severe paroxysms of coughing during the night, accompanied by a well defined whoop strongly suggestive of pertussis. Usually, the child did not awaken. There was no coughing whatever during the day and there was no vomiting at any time. These symptoms persisted for about a month and gradually subsided. At times there was a rise of two or three degrees in temperature, but this is of doubtful significance, because there was also a mild pyelitis which yielded to sodium bicarbonate treatment and was probably an independent infection.

On April 27 a throat swab from the child was cultured on blood agar. Nothing regarded as significant appeared except a few very delicate colonies of a small Gram-negative hemoglobinophilic influenza-like bacillus. They were not *B. pertussis* nor the organism isolated later. During the night of April 29 a plate of "chocolate" blood-agar was exposed within 2 inches of the child's mouth during a paroxysm of coughing. Twenty-five per cent of the colonies which grew on this plate were small greyish semi-transparent flatly convex colonies, without apparent alteration of the surrounding medium, and composed of small Gram-negative actively motile bacilli to be described. During the night of May 14 another plate of chocolate blood-agar was similarly exposed and about sixty per cent of the colonies that developed were of the same organism iso-

lated on April 29. Soon after this the coughing ceased and there were no more opportunities to isolate the organism in this way.

Study of the strains isolated on April 29 showed them to be culturally similar to *B. bronchisepticus* and served to direct suspicion to the pet rabbit as a possible source of infection. On May 4 a blood agar plate was streaked with a swab from the nares of the rabbit immediately after taking the swab. There developed on the plate an abundant growth, mostly *B. bronchisepticus*. A second plate inoculated several hours later from the same swab after it had been carried to the laboratory showed none of this organism. On May 6 the rabbit was brought to the laboratory and cultures were again made from material obtained by inserting a platinum loop deep into the nostril, care being taken not to touch the external nasal opening. There developed an abundant growth of *B. bronchisepticus* in pure culture. On May 8 the rabbit was found dead as the result of an accident. It had caught its hind foot in a hay-rack near the top of the cage and had hung until dead. Apparently it had not been dead long, It was autopsied at once. In gross appearance the lungs were normal. The trachea and bronchi contained a small amount of muco-purulent material which, when stained with Loeffler's methylene blue, showed many very small bacilli. The other organs were apparently normal. Sections of the lung stained with eosin and methylene blue by Mallory's (1912) method showed in the bronchi a small amount of exudate containing few leucocytes but many desquamated epithelial cells and large numbers of minute bacilli. Here and there in the cilia of the epithelium lining the bronchi were collections of small bacilli often lined up in rows between the cilia. The alveoli did not appear to be invaded by the bacilli and the lung substance appeared normal except for a slight congestion, possibly hypostatic, since the animal had died hanging by a hind foot. A blood-agar plate inoculated with a loop of material from the bronchus at autopsy developed an abundant growth of *B. bronchisepticus* in almost pure culture. *Pasteurella cuniculicida* was looked for but not found.

The organisms isolated at various times from the child and from the rabbit and a strain of *B. bronchisepticus* obtained from the stock

collection of the Society of American Bacteriologists were alike in every respect; indistinguishable one from another.

Morphologically the organisms were very small bacilli usually occurring singly, less commonly in pairs. In a young broth culture they measure about 0.5 by 0.7 to 1.5 micra; longer forms appearing as the culture becomes older. On blood agar the bacilli are more coccoid. Young cultures in either fluid or solid media are actively motile. No capsules could be found in moist ink preparations. The bacilli are Gram-negative.

On the surface of blood agar individual colonies are small and round but, where crowded, they readily form streaks of glistening, milky, semi-transparent, confluent growth. There is no apparent hemolysis or discoloration about individual colonies, but there may be an indefinitely defined area of hemolysis beneath thicker areas of growth. Deep colonies are small and biconvex without zones of hemolysis or discoloration. If the plate is thickly seeded, sooner or later hemolysis appears throughout and an odor that is ammoniacal.

In deep shake agar cultures growth is most abundant at the surface. The deep colonies, most conspicuous very near the surface, are very small, most of them being visible only with the aid of a strong lens.

Infusion broth is well clouded within 24 hours. There appears a delicate surface ring and then fragments of delicate pellicle. As the culture becomes older, a ropy sediment forms. Old broth cultures, when boiled, exhibit the phenomenon described by Smith (1913). On boiling they become very viscid. A few drops of acetic acid causes the viscid material to separate out as a mucoid mass, which on shaking becomes flocculent. No capsule could be demonstrated.

In dextrose broth no acid is produced, the reaction becoming strongly alkaline.

In milk containing brom-cresol purple there is no coagulation and no acidity is developed. Within 24 hours the upper layer of milk becomes purple and after several days the alkali has spread downward until the whole medium is deeply purple. There is no apparent digestion.

On potato there is an abundant mucoid growth at first yellow and then gradually becoming tan, similar to the "honey-like" growth of the glanders bacillus.

Rabbits were immunized by intravenous injections of killed cultures of the strains from the child, the rabbit, and the stock strain of *B. bronchisepticus*. Half-grown rabbits were used after titrating their sera for agglutinins against the strains mentioned. A summary of the results of agglutinin titrations before and after immunization is given in table I. The numerical values indicate the highest dilutions of sera which gave distinct agglutination after incubation of the tubes for two hours at 37°C. and refrigeration over night. Rab-

bit 108 was immunized against the stock strain of *B. bronchisepticus;* Rabbit 112 against the human strain; Rabbit 113 against the rabbit strain. None of the strains showed spontaneous agglutination in salt solution controls.

None of the immune sera agglutinated a stock strain of *B. pertussis* in dilutions higher than 1/50 or 1/100.

TABLE I

Titration of agglutinins in sera of rabbits before and after immunization

CULTURE	RABBIT NUMBER	AGGLUTININ TITER OF SERA	
		Before immunization	After immunization
Stock strain of *B. bronchisepticus*	108	1/50	1/3200
	112	1/100	1/12800
	113	1/200	1/6400
Human strain	108	1/25	1/3200
	112	1/50	1/6400
	113	1/50	1/6400
Rabbit strain	108	1/25	1/3200
	112	1/100	1/6400
	113	1/50	1/6400

DISCUSSION

As a result of the work of Ferry (1910, 1911, 1912), M'Gowan (1911), and Torrey and Rahe (1912) *B. bronchisepticus* is generally accepted as the cause of canine distemper. The same organism was found to produce similar natural infections of cats, rabbits and guinea-pigs. Both M'Gowan (1911) and Ferry (1912) found the organism a number of times in monkeys, and M'Gowan found it in ferrets, in a goat, and once in a man. Smith (1913) described the organism as a cause of pneumonia in guinea-pigs. M'Gowan has given the only fully reported case of human infection with *B. bronchisepticus* that I have found in the literature, although Ferry (1917) mentions that the organism has been isolated from the human subject by himself and by the New York Board of Health Laboratory. M'Gowan's case was one of very irritating chronic nasal catarrh in a man constantly handling rabbits and guinea-pigs for one and a half years in

the laboratory. Ferry in a personal communication to the author writes that his case was that of a laboratory worker whose duty it was to test diphtheria antitoxin on guinea-pigs at a time when they were having trouble with *B. bronchisepticus* infection. The patient had a typical case of "grippe"—cough, headache, backache, and fever. The sputa gave a pure culture of *B. bronchisepticus*.

In 1912 Mallory and Hornor described the presence of masses of minute bacilli between the cilia of the epithelial cells of the respiratory passages as the characteristic lesion of pertussis. They considered the action of the bacilli to be largely mechanical, interfering with the normal movements of the cilia, preventing the normal removal of secretion and of inhaled particles, and thus producing an irritation which results in coughing and usually also in the characteristic spasm known as whooping. A little later Mallory, Hornor and Henderson (1913) described similar lesions in puppies and rabbits which they had inoculated intra-tracheally with sputa and pure cultures from pertussis cases and with a culture of the Bordet-Gengou organism obtained from a commercial laboratory, and said to have been obtained originally from Bordet. In a discussion of Mallory's paper read before the Massachusetts Medical Society (July, 1913) Rhea pointed out that a similar lesion was to be found in dogs with distemper. He said:

> Besides this inflammatory reaction there are in the cilia of the epithelial cells of the respiratory tract very many small organisms which I have been unable to distinguish morphologically from the Bordet-Gengou bacillus.

He also described a similar lesion in rabbits suffering from snuffles. Smith (1913) described the same lesion in guinea-pigs infected with *B. bronchisepticus* and concluded:

> This and other evidence makes it highly probable that the bacilli found by Mallory in the respiratory tract of animals treated with *B. pertussis* of Bordet were *B. bronchisepticus*.

Mallory (1913), in a paper reviewing his own work and quoting the observations made by Rhea, adds:

> Dr. L. W. Gorham has recently repeated some of the experimental work, starting with a new culture of the whooping cough bacillus obtained from an acute case of

the disease. He used six young rabbits from one litter. Two were inoculated daily for a week with a suspension of the whooping cough bacillus. They lost weight and died at the end of ten days. Two others were inoculated in the same way with the influenza bacillus, one with the pyocyaneus, and one with normal salt solution. These four were killed at the end of ten days. Sections of the nares, trachea and bronchi from the two animals inoculated with the whooping cough bacillus showed great numbers of minute bacilli between the cilia. Pure cultures were obtained from one of the animals; but it was the *Bacillus bronchisepticus*, not the *Bacillus pertussis*. Cultures from the other rabbit were badly contaminated. Cultures and sections from the four other animals from the same litter were entirely negative so far as the *Bacillus bronchisepticus* was concerned.

Since the lesions found in pertussis are like those found in animals with *B. bronchisepticus* infection, our finding this organism in a child with the clinical symptoms of whooping cough adds weight to Mallory's view that the symptoms of pertussis are largely due to the mechanical action of the bacilli in the cilia of the respiratory tract. Except in the possession of flagella, *B. bronchisepticus* is morphologically similar to *B. pertussis*. Except for their growth in litmus or brom-cresol purple milk and on potato, they resemble each other culturally after they are isolated. *B. bronchisepticus* is much the more easily isolated. Mallory succeeded in isolating the organism he worked with from only a few of the cases studied. As a control culture he used a strain supposed to be *B. pertussis* from a commercial laboratory. A strain which Smith (1913) obtained from a commercial laboratory proved to be *B. bronchisepticus*. Our finding this organism in a child with symptoms of whooping cough suggests the possibility that the strains which Mallory succeeded in isolating may have been from similar cases and that the infections which he found in inoculated animals were actually due to the organisms injected. Graham's results with the six young rabbits of the same litter are most easily interpreted in this way.

CONCLUSION

The close association of children with pet animals and the wide prevalence of *B. bronchisepticus* infection among these animals would indicate that human infection with this organism may be more common than has been recognized. It is not known whether the infection is readily transmitted from one child to another, but an inter-

esting public health and epidemiological problem is involved. It may be that in many supposed cases of pertussis the patients are needlessly quarantined, and it may be that if cases of *B. bronchisepticus* infection were correctly diagnosed there would be fewer cases of pertussis without a history of exposure to other cases.

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BOOK REVIEWS

Diseases of the Gums and Oral Mucous Membrane. By Sir Kenneth Goadby. Oxford Medical Publication. (*Henry Frowde; Hodder and Stoughton, London, 1923.*)

This is probably the first work of its kind published, that deals with its subject comprehensively, intelligently and clearly.

The chapter on the physiology, anatomy and pathology of the gums should be of particular interest to the practitioner of medicine, while the methods of treatment, both surgical and medical, should also prove of great value to the dentist.

One can hardly subscribe to all of the theories advanced in the chapter on "Diseases Originating from Mouth Affections"; some of them are not entirely convincing. On the whole, however, the chapter is a good one, particularly the part dealing with latent or quiescent chronic infection.

The last chapter on vaccines is very timely and well written, and we agree with the author that, when properly prepared and administered, they occupy a large place in therapeutics, in oral as well as in other infections.

The work, as a whole, is by far the best that we have seen on the subject. It should occupy a prominent place in the library of the physician and dentist and could very well be used as a textbook by students of both professions. It is well written, in clear concise terms, and profusely illustrated.

L. D. C.

Bailey's Text-book of Histology. Revised by O. S. Strong and A. Elwyn. 7th ed. 939 + xviii pp. $7.00. (*New York, William Wood and Company, 1925.*)

The revision of this well-known textbook presents a complete reconsideration of the nervous system and little change in microscopic anatomy.

In the latter the subjects of reticulo-endothelium and blood include many modern studies with a certain definite bias. And yet mesothelium and endothelium are classified as simple epithelia, tissues in no way physiologically similar. The chapters on the stomach and pancreas are rather inadequate. Neither Bensley's work upon the glands of the stomach nor his classical studies on the pancreas are mentioned. Nothing new is discussed on the lung, kidney or testes, a criticism which does not hold for the ovary or hypophysis. There is scant consideration of cellular potentialities, without which there can be no real understanding of tissue. The style is dogmatic. There is no bibliography of original papers.

The section on neurology is well presented and copiously illustrated, with many original photographs and diagrams. It furnishes, better than any other English textbook, a real anatomical basis for the consideration of function. The

introduction will orient the student. The classification of centers in the medulla follows closely that of the physiologist. The contributions of the war to the understanding of the cortex are included for the first time in an anatomy of the nervous system.

Although the author gives in concise form what is known of the subject, he does not separate technique, data and deduction in such a way that the student may learn to think on these things for himself. Consequently, the work does not offer a point of departure for further inquiry. And yet as a textbook of neurology it can be unqualifiedly recommended to beginning students.

M. H. L.

Neurological Fragments. By J. HUGHLINGS JACKSON. 227 pp. $3.75. (*Humphrey Milford, Oxford University Press, London, 1925.*)

Under this title is included a collection of twenty-one papers in which Jackson has discussed various neurological problems of particular importance. To Dr. James Taylor we owe our indebtedness, not only for this very successful compilation, but also for the interesting biological memoir. And the "Recollections" of Hughlings Jackson, by Sir Jonathan Hutchinson and Dr. Mercier, add many important facts which help the reader to a better understanding of his character and genius.

Graduating in 1860 Dr. Jackson first associated himself with the London Hospital. A few years later he entered the National Hospital and was brought into contact with Brown-Séquard, through whose influence he gradually devoted himself to problems connected with the nervous system. Always attracted by the convulsive states, he subsequently became particularly interested in the localized forms of epilepsy, with which his name eventually became so inseparably connected.

Following a lecture delivered before the Hunterian Society in 1892 on "Neurological Fragments" in which was discussed in a brief and characteristic manner a number of isolated questions, such as, the delirium of pneumonia and its relation to supervenous blood, asphyxia fits in rickets, cerebral fever, and transverse lesions of the cord, Dr. Jackson began a series of papers in which his wide experience and trained observation were devoted to recording and discussing neurological questions, of clinical or physiological interest.

In his first paper he had an opportunity of considering a subject in which neurological circles at the time were concerned. Mendel, after experimenting with Gudden's method on rabbits and guinea-pigs, had advanced the theory that the oculo-facial group of muscles was innervated by the oculo-motor nucleus. In a report on two cases of ophthalmoplegia externa Jackson demonstrated a paresis of the orbicularis palpebrarum, so that clinically he was able to support this hypothesis.

Space does not permit of a complete review, but the subsequent papers include: The recommendation of cocaine in the examination of the eyes, as being less disturbing than the ordinary mydriatics, as well as for its usefulness in studying the

muscles supplied by the sympathetic, and the condition of the knee-jerk in supervenosity and opium poisoning. An interesting account is given of the surgical technique of twenty years ago, in the case of a left temporo-sphenoidal abscess producing a right-sided hemiplegia, lateral deviation of the eyes and aphasia, with recovery. Three papers deal with the lateral deviation of the eyes, and include a discussion of Dr. Risien Russell's researches on the representation of various ocular movements in the cerebral cortex. Two papers are devoted to a discussion of epilepsy with auditory warnings. Two interesting cases are reported of fits, following the touching of the head. In several papers the value of dividing the central nervous system into lower, middle, and higher sensory-motor levels is argued, followed by a consideration of the question by Sherrington and Bastian. This division, while admittedly provisional and incomplete, is nevertheless very instructive and interesting. Finally, certain abnormalities of sensation of cerebral origin are dealt with.

The unusual value of these contributions attracted a wide-spread interest, which culminated in a request by Dr. Osler, Dr. Weir Mitchell and Dr. James Putnam, that a collection of them should be reprinted. It was Dr. Jackson's intention to attempt this, but ill health set in and he never really commenced.

These papers illustrate in a remarkable manner the extraordinary interest that Dr. Jackson took in any neurological problem. The carefulness and detail of his reports and his meticulous veracity are evidence of his thoroughness and devotion to his work. The clearness and precision of his explanations are illuminating, and though some of his views differ from those held today, the book is strongly to be recommended to the thoughtful student.

A. T. M.

Insulin. By W. R. CAMPBELL and J. J. R. MACLEOD. 242 pp. $4.00. (*The Williams & Wilkins Company, Balto., 1925.*)

This book is an expansion of the review on insulin which appeared last year in *Medicine.* It is divided into two parts. Part I is entitled "Physiology" and is written by Professor J. J. R. Macleod. It contains sixty-four pages and is a summary of the work done to date on insulin, with particular stress on the studies which have been carried out during the last four years in the University of Toronto. Such a résumé of the physiology of insulin necessarily suffers from omissions of important material because of the enormous activity of workers in the field and because of the many fresh papers which are constantly appearing. One may regret that no mention is made of two outstanding recent contributions—the work of Abel and Geiling on the relation of labile sulphur to insulin, and that of Lundsgaard and Holvoll on the mutorotation of glucose under the influence of insulin and muscle juice.

Part II is called the Clinical Section and contains 165 pages by Dr. W. R. Campbell. To this are appended about 40 pages of food recipes, tables of food equivalents and analyses. The methods of treating diabetes which are outlined are in general accord with modern practice in American clinics, and stress is properly

laid on the position of prime importance which diet holds in therapy. Yet another formula is given for calculating ketogenic-antiketogenic ratios. It is a matter of interesting speculation as to just how many such formulas and variations of formulas will have to appear before the opinions of all writers on the subject will finally be expressed.

In conclusion, it is the opinion of the reviewer that the clinical section of the book is distinctly disappointing and that the attempt has been made to cover altogether too much ground and to meet too many needs in the number of pages allotted. The volume contains a good bibliography.

G. A. H.

Selected Papers, Surgical and Pathological. By F. T. PAUL, D.Sc. Liverp. (Hon.), Ch.M., Liverp., F.R.C.S., Eng., Consulting Surgeon, Liverpool Royal Infirmary. 284 pp. 15/–. (*London, Baillière, Tindall and Cox, 1925.*)

This volume covers a period of approximately fifty years, during which surgery made rapid and remarkable progress. The papers represent an important contribution to the advancement of both surgery and pathology. It is interesting to note the marked improvement in the technique and surgical judgment between the author's early and later papers. This no doubt can be attributed to his histological, pathological and experimental researches. Some of the conclusions have been found faulty, but on the whole the vast majority of the work has proven to be fundamentally sound and generally accepted.

W. D. N.

Psychological Healing. By PIERRE JANET, Professor of Psychology at the College of France. Translated from the French by Eden and Cedar Paul. Two vols. Pp. 1265. (*New York, The Macmillan Company, 1925.*)

This work is an historical and critical study of all of the more important modern systems of psychotherapeutics. However, the various methods are described and evaluated only as they relate to the treatment of hysteria and psychasthenia.

The first volume is devoted to a consideration of psychological methods which serve to utilize automatisms or to conserve the energies of the patient's personality. In this connection, miraculous healings, Christian Science, and medical moralization (the method of Dubois) are described as special procedures from which motivation to new attempts at adjustment are derived. Suggestion and hypnotism are described as serving effectively a somewhat similar function. In connection with methods which aim primarily at conservation of energy and resources, emphasis is placed on the Mitchell system of rest, on "isolation" as reducing the energy expenditure incidental to social intercourse, and on mental liquidation of traumatic memories as practiced by Freud and others.

The second volume is devoted to a study of psychotherapeutic methods which serve to develop useful tendencies existing in the individual, or which originate entirely new assets. Education and re-education are described, but greater attention is devoted to "Treatment by Excitation," especially "Excitation by

completed successful actions." Dr. Janet is impressed by the regularity with which psychopaths seek sources of excitement and by the favorable effects which are sometimes secured through exciting experiences. This leads him to advocate what he seems to consider a novel method, namely, the subjection of patients to sources of excitation which enable them to complete actions. The second volume also includes an extended discussion of "moral guidance," and the author appears to advocate the deliberate attachment of the patient to the physician. The dangers of such dependence are not adequately recognized.

Dr. Janet employs a uniform method in discussing each system of therapeusis. Attention is first given to the history of the development of the technique, with a discussion of such success as has been achieved in application. A psychological analysis of the particular method follows and an attempt is made to indicate the characteristics of the patients who are favorably affected by it. Finally, a searching criticism is made. Dr. Janet distinguishes himself from most of the writers in the field by finding some virtue in each of the therapeutic methods which he describes. The problem of psychiatry he believes to consist in discovering the diagnostic signs which indicate the method of treatment which can be most effectively employed.

From his criticisms and from occasional direct exposition it is possible to discover the author's opinion of the fundamental nature of hysteria and psychasthenia. He appears to regard both as conditions of "reduced psychological tension" by reason of which the patient is unable to react to his environment with the higher forms of mental activity. Such reduction of tension is due to exhaustion or emotion, and treatment to be effective must raise the tension.

As an historical study by an authority who is relatively unbiased, the work is invaluable. The critical features, while important, would be considerably more effective if the author's own psychological position were more modern. He is apparently unfamiliar with the simple primary psychological processes which have been demonstrated and described by American and Russian psychologists, especially conditioned emotional reactions and emotional diffusion. He also clings to the concept of "disease process" and "symptoms," not appreciating the value of Dr. Adolph Meyer's psychobiological point of view.

E. B.

International Clinics. Ed. by Henry W. Cattell, A.M., M.D., and Charles H. Mayo, M.D. (*et al.*), vol. iii, Thirty-fifth Series. $2.00. (*J. B. Lippincott Co., Philadelphia and London, 1925.*)

The twenty-seven articles which make up this volume of the International Clinics cover such a wide range of subjects that it is difficult to judge the value of the book. While some of the articles will interest physicians engaged in general practice, others such as "The Pathological Histology of the Lachrymal Sac in Chronic Purulent Dacrocystitis" will attract only those whose work is quite specialized. On the whole, the articles on medical topics have more merit than those devoted to surgery.

Major Dunham's article on Variation in Blood-pressure as associated with variation in Age and Body-weight, and Major White's on Basal Metabolism, deserve particular mention both because of their methods of presentation and because the conclusions drawn are based on such a large number of observations.

Jablon's monograph on thrombo-angitis obliterans stands out in this volume as the contribution of greatest value. This subject is considered in a very comprehensive and, yet, interesting manner. The author's results obtained by the intravenous use of a specially prepared solution of sodium citrate in normal saline are very encouraging. Numerous plates illustrate the described conditions and the bibliography, at the end of the article, should be of great help to anyone interested in this subject.

L. B.

Chemistry of the Blood in Clinical Medicine. By O. L. V. DE WESSELOW. 255 pp. $4.50. (*Wm. Wood and Company.*)

The stated purpose of this book written by the Chemical Pathologist to St. Thomas's Hospital, London, is to furnish some knowledge of the main facts of the chemistry of the blood for the use of general practitioners, and to describe concisely those aspects of the subject that are of interest to the clinician. The author gives credit largely for the development of clinical methods to American workers. The book contains a somewhat comprehensive and doubtless useful survey of the subject. A great deal of ground is covered in the two hundred and fifty-five pages but by no means all of it is very carefully covered. The references are scanty, often poorly chosen, and there are a number of inaccuracies. The discussion on blood sugar is rather inadequate and it is unfortunate that the changes in the blood which follow the use of insulin are not more clearly dealt with. One would think that "blood chemistry" has no more practical information to offer the general practitioner than a knowledge of these.

The treatment of anoxemia is inadequate and lacks clearness. It is annoying to note that Herter is given sole credit for the development of the technique of arterial puncture. This method was rescued from complete obscurity and demonstrated as a practical clinical procedure by Stadie. There are a number of such errors in the book.

An appendix furnishes a description of several blood methods, but the one given for blood sugar is not the simplest for the use of the "general practitioner." The older method given for chlorides by Van Slyke has been subjected by its originator to recent important improvements which are not mentioned; the directions for the method of phosphate determination are inadequate.

Possibly, the deepest impression that one carries away from a perusal of this book, which is no worse but certainly no better than half a dozen others on the same subject that have appeared in the last three or four years, is the real need for a well balanced, concise and thoroughly modernized treatise on this subject from the point of view of its practical clinical applications, and it is gratifying to learn that such a volume is shortly to appear from the pen of one our most distinguished American workers.

G. A. H.

Pernicious Anemia and Hemolytic Anemia. By ARTHUR SHEARD. 94 pp. $2.50. (*William Wood & Co., New York. 1925.*)

This little book, based on an analysis of a number of cases of pernicious anemia and one case of aplastic anemia, gives an interesting summary of the present status of knowledge of these diseases.

The presentation is attractive but it is only fair to say that no information which is not already easily accessible in text-books and monographs is brought out.

A. L. B.

BOOKS RECEIVED

Bailey's Text-Book of Histology. Revised and rewritten by Oliver S. Strong, A.M., Ph.D., and Adolph Elwyn, A.M. Seventh edition, profusely illustrated. 1925. 8°. 939 pages. William Wood and Company, New York. $7.00.

Insects and Diseases of Man. By CARROLL FOX, M.D. With 92 illustrations. 1925. 8°. 349 pages. P. Blakiston's Son & Co., Philadelphia. $4.00.

Insulin. Its Use in the Treatment of Diabetes. Part I—Physiology, by J. J. R. MACLEOD. Part II—Clinical Section, by W. R. CAMPBELL. Medicine Monographs, Volume VI. 1925. 8°. 242 pages. The Williams & Wilkins Company, Baltimore. $4.00

Psychological Healing. A Historical and Clinical Study. By PIERRE JANET. Translated from the French by Eden and Cedar Paul. In two volumes. 1925. 8°. 1265 pages. The Macmillan Company, New York.

The Medical Department of the United States Army in the World War. Volume XV. Statistics. Part two. Medical and Casualty Statistics. Based on the Medical Records of the United States Army, April 1, 1917, to December 31, 1919, inclusive. Prepared under the direction of Maj. Gen. M. W. Ireland, the Surgeon General. By Maj. Albert G. Love, M.C., U. S. Army. 1925. 8°. 1386 pages. Government Printing Office, Washington, D. C.

Chemical Pathology. Being a Discussion of General Pathology from the Standpoint of the Chemical Processes involved. By H. GIDEON WELLS, Ph.D., M.D., Fifth edition, revised and reset. 1925. 8°. 790 pages. W. B. Saunders Company, Philadelphia and London. $8.50.

The Therapy of Puerperal Fever. By PRIVATDOZENT DR. ROBERT KOEHLER. American edition prepared by Hugo Ehrenfest, M.D., F.A.C.S. With twenty-seven illustrations. 1925. 8°. 276 pages. The C. V. Mosby Company, St. Louis. $4.00.

Applied Biochemistry. By WITHROW MORSE. 1925. 8°. 958 pages. W. B. Saunders Company, Philadelphia and London. $7.00.

A Textbook of Physiology. By WILLIAM D. ZOETHOUT, Ph.D. Second edition, 1925. 8°. 616 pages. The C. V. Mosby Company, St. Louis. $4.50.

Thoracic Surgery. The Surgical Treatment of Thoracic Disease. By HOWARD LILIENTHAL, M.D., F.A.C.S. In two volumes with 904 illustrations, 13 in colors. 1925. 8°. 694 & 600 pages. W. B. Saunders Company, Philadelphia and London. $20.00

Massage and Therapeutic Exercise. By MARY MCMILLAN. Second edition, reset. 1925. 12°. 331 pages. W. B. Saunders Company, Philadelphia and London. $2.50.

Development of Our Knowledge of Tuberculosis. By LAWRENCE F. FLICK, M.D., LL.D. 1925. 8°. 783 pages. Philadelphia. $7.50.

Étude sur la Vieillesse et le Rajeunissement par la Greffe. Par le DR. SERGE VORONOFF. Avec 35 planches hors texte. 1926. 8°. 213 pages. Gaston Doin, Paris.

Physiotherapy Theory and Clinical Application. By HARRY EATON STEWART, M.D. 1925. 8°. 351 pages. Paul B. Hoeber, New York. $7.50.

The Harvey Lectures. Delivered under the auspices of the Harvey Society of New York under the patronage of the New York Academy of Medicine. By DR. A. BIEDE, DR. WALTER R. BLOOR, [*et al.*] Series XIX, 1923–1924. 1925. 8°. 254 pages. J. B. Lippincott Company, Philadelphia. $3.50.

Saint Bartholomew's Hospital Reports. Edited by W. McAdam Eccles, Sir Thomas Horder, Bart. [*et al.*] Vol. lviii, 1925. 8°. 113 pages. John Murray, London.

Modern Medicine. Its Theory and Practice. In original contributions by American and foreign authors. Edited by Sir William Osler, Bart., M.D., F.R.S. Third edition, thoroughly revised. Re-edited by Thomas McCrae, M.D. Assisted by Elmer H. Funk, M.D. Volume 1. Bacterial Diseases—Non-Bacterial Fungus Infections—The Mycoses. Illustrated. 1925. 8°. 845 pages. Lea & Febiger, Philadelphia and New York. $9.00

Skull Fractures. Roentgenologically Considered. Eighty-three Roentgen ray studies on forty-four full page plates and forty-nine text illustrations. By WILLIAM H. STEWART, M.D. With surgical comments by William H. Luckett, M.D. 1925. 4°. 64 pages. Paul B. Hoeber, New York. $12.00.

University of Pennsylvania. Eighteenth Report of the Henry Phipps Institute for the Study, Treatment and Prevention of Tuberculosis. 1925. 8°. 274 pages. Philadelphia.

Investigations into d'Herelle's Phenomenon. By ERNST GJORUP. 1925. 8°. 156 pages. Arnold Busck, Copenhagen.

New York State Department of Health. Studies from the Division of Laboratories and Research. Augustus B. Wadsworth, M.D., Director. Reprints, 1923–1925. Albany, New York.

Selected Papers, Surgical and Pathological. By F. T. PAUL, D.Sc., Liverp. (Hon. Caus.), Ch.M., Liverp. F.R.C.S. Eng. 1925. 8°. 284 pages. Baillière, Tindall and Cox, London. 15/.

William Cadogan. [*His Essay on Gout.*] By JOHN RUHRÄH, M.D. 1925. 12°. 114 pages. Paul. B. Hoeber, New York. $1.50.

A Text-Book of Medical Diagnosis. By JAMES M. ANDERS, M.D., Ph.D., LL.D., and L. NAPOLEON BOSTON, A.M., M.D. Third edition, entirely reset with 555 illustrations, 21 in colors. 1925. 8°. 1422 pages. W. B. Saunders Company, Philadelphia and London. $12.00.

Intravenous Therapy. Its Application in the Modern Practice of Medicine. By WALTON FOREST DUTTON, M.D. Illustrated with 64 half-tones and line engravings, some in colors. Second revised and enlarged edition, 1925. 8°. 594 pages. F. A. Davis Company, Philadelphia. $6.00.

Connecticut State Medical Society. Proceedings. 133d Annual meeting. Editor Charles Williams Comfort, Jr., M.D. 1925. 8°. 404 pages. Published by the Society.

U. S. War Department. Report of the Surgeon General, U. S. Army, to the Secretary of War. 1925. 8°. 483 pages. Government Printing Office, Washington.

Radiography. A Manual of X-Ray Technique, Interpretation and Therapy. By CHARLES D. ENFIELD, M.D., F.A.C.P. 194 illustrations. 1925. 4°. 299 pages. P. Blakiston's Son & Co., Philadelphia. $10.00.

Experimental Investigations into the Emotional Life of the Child. Compared with that of the Adult. By HELGA ENG. Translated by George H. Morrison, M.B. (Edin.) 1925. 8°. 243 pages. Humphrey Milford, London. $6.50.

Abdominal and Pelvic Surgery for Practitioners. By RUTHERFORD MORISON, Hon. M.A. & D.C.L., Hon. LL.D., M.B., F.R.C.S. (Ed. and Eng.) 1925. 12°. 212 pages. Oxford Medical Publications. Humphrey Milford, Oxford University Press, London. $2.75.

Post-Mortem Appearances. By JOAN M. ROSS, M.B., B.S. (Lond.), M.R.C.S., L.R.C.P. With preface by E. H. Kettle, M.D. 1925. 15°. 216 pages. Oxford Medical Publications. Humphrey Milford, Oxford University Press, London. $2.50.

International Clinics. A Quarterly of Illustrated Clinical Lectures and Especially Prepared Original Articles. Edited by Henry W. Cattell, A.M., M.D. with the collaboration of Chas. H. Mayo, M.D. Thirty-fifth series, volume iv. 1925. 8°. 311 pages. J. B. Lippincott Company, Philadelphia and London. $2.50.

Who's Who in American Medicine. Editors: Lloyd Thompson, M.D., F.A.C.P., and Winfield Scott Downs. 1925. 12°. 1820 pages. Who's Who Publications, New York. $10.00.